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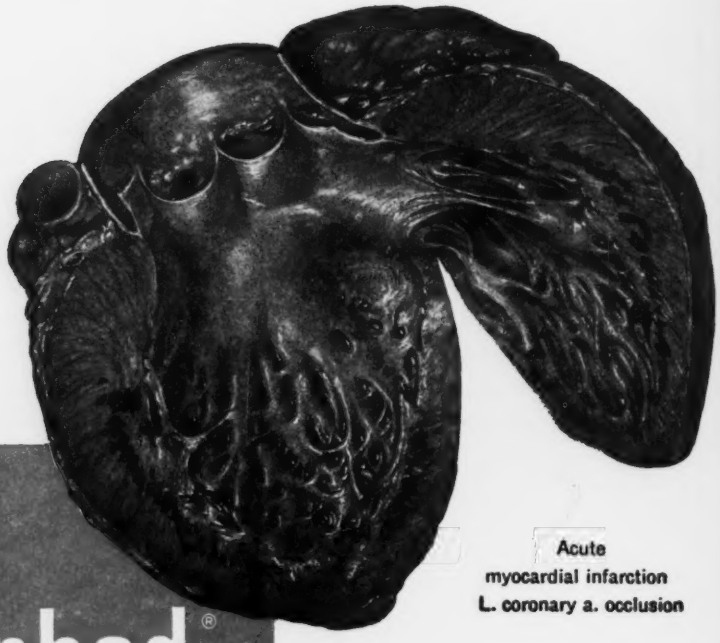

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Chemical Quantitation of Epinephrine and Norepinephrine in Thirteen Patients with Pheochromocytoma

By WILLIAM M. MANGER, M.D., EUNICE V. FLOCK, PH.D., JOSEPH BERKSON, M.D., JESSE L. BOLLMAN, M.D., GRACE M. ROTH, PH.D., EDWARD J. BALDES, PH.D., AND MARTIN JACOBS

Fluorescent quantitation of epinephrine and norepinephrine in plasma of patients suspected of having pheochromocytomas is of considerable diagnostic value. The concentrations of these pressor amines in normal subjects, patients with various diseases with and without hypertension, and 13 patients with pheochromocytomas are reported. In all patients with pheochromocytomas and sustained hypertension the concentrations of pressor amines were significantly elevated. However, in patients with paroxysmal hypertension secondary to pheochromocytomas the pressor amine concentrations may be unelevated when the blood pressures are normal. In this latter group provocative tests with intravenous histamine are indicated to induce hypertension prior to quantitating pressor amines.

WITH a chemical method available for estimating the concentration of epinephrine and norepinephrine in plasma,[1, 2] it has been possible to quantitate these pressor amines in 13 patients with pheochromocytomas. Initially in this study, the method of Weil-Malherbe and Bone,[1] which consists of alumina adsorption of the pressor amines from plasma followed by elution with acetic acid and condensation with ethylenediamine, was used to obtain a measurable fluorescence. Since this method allowed only the estimation of the concentration of total pressor amines (that is, "adrenalinelike" substance), we devised a modification[2] that consists in the use of sodium thiosulfate, which affects differentially the fluorescence of epinephrine and norepinephrine, thus enabling the quantitation of each. According to Weil-Malherbe and Bone,[3] it has been established that the fluorescent substances estimated in the blood of normal human subjects are "identical with adrenergic amines in their affinity to amine oxidase in R_F values and in the fluorescence spectra of their derivatives." However, it is possible that in some disease states, particularly where there is associated azotemia, there may be a significant retention of fluorescent substances other than the pressor catechols which could cause erroneous calculations.

The concentration of epinephrine and norepinephrine in venous plasma was estimated unless otherwise indicated, and it was not required that patients be fasting when blood was obtained. Concentrations are expressed in micrograms per liter of plasma (1) of "epinephrinelike substance" and (2) of epinephrine and norepinephrine individually. The estimate of "epinephrinelike substance" refers to the concentration equivalent of the fluorescence

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Abridgment of portion of thesis submitted by Dr. Manger to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Medicine.

TABLE 1.—*Normal Subjects*

Subject	Concentrations, μg./liter plasma		
	Epinephrine-like substance*	Epinephrine†	Norepinephrine
1	2.0		
2	2.0		
3	2.2		
4	2.5		
5	1.6	0	5.2
6	1.7	0	6.2
7	1.3	0.2	3.6
8	1.6	0.6	3.3
9	1.2	0	4.6
10	0.3	0.1	0.8
11	1.4	0.1	4.0
Mean	1.62	0.14	3.96
Range	0.3–2.5	0–0.6	0.8–6.2
Standard deviation	0.59	0.21	1.7

* This is the equivalent of the fluorescence reading (before addition of $Na_2S_2O_3$) if it were due entirely to epinephrine. It is equal to the epinephrine plus 0.316 times the norepinephrine.

† When calculated values (equation 5, ref. 2) were less than zero (due to errors intrinsic in the method when small quantities are involved) the concentration of epinephrine was recorded as 0.

reading before addition of sodium thiosulfate were it all due to epinephrine. The fluorescence is usually due to both epinephrine and norepinephrine, but since norepinephrine exhibits only about a third of the fluorescence that epinephrine does, the recorded concentration of "epinephrinelike substance" is less then the sum of the recorded epinephrine and norepinephrine. This term "epinephrinelike" (or "adrenalinelike") was first introduced by Weil-Malherbe and Bone[1] and has been retained, since many such determinations were performed before a method of estimating the individual concentrations of epinephrine and norepinephrine had been devised.

RESULTS IN NORMAL SUBJECTS

The plasma concentrations of pressor amines in 11 normal subjects without hypertension are recorded in table 1. The concentration of "epinephrinelike" substance was never found to exceed 2.5 μg. per liter, and this was almost entirely norepinephrine with little if any epinephrine. The mean concentration of "epinephrinelike substance" was 1.6 μg. per liter.* However, from the analysis of large quantities of plasma by the method of paper chromatography followed by elution and fluorometric quantitation, it appears that a small percentage of fluorescence in normal plasma may be due to substances other than epinephrine and norepinephrine.

* Weil-Malherbe and Bone[1] reported a mean concentration of approximately 3 μg. per liter.

RESULTS IN PATIENTS WITHOUT PHEOCHROMOCYTOMA

In table 2 are recorded the plasma concentrations in 25 patients without pheochromocytomas. As indicated, most of these patients had hypertension—either primary or associated secondarily with their disease process. Many of these patients were chosen for study because some of their symptoms, signs and laboratory findings may simulate those in patients with pheochromocytomas. It is noted that the highest value for epinephrinelike substance was 3.1 μg. per liter and that the sum of epinephrine and norepinephrine was never more than 11.2 μg. per liter. The latter concentration occurred in a patient with renal hypertension and blood urea of 196 mg. per 100 ml. It is possible that in this patient, and in two other patients with essential or renal hypertension and blood ureas of 342 and 122 mg. per 100 ml. respectively, retention of catechols other than epinephrine and norepinephrine accounts in part for the high values of pressor amines. In all the other patients, the blood ureas, when determined, were essentially normal. If the patients with azotemia are excluded from the series, it is noted that the sums of epinephrine and norepinephrine for all the subjects are less than 8 μg. per liter. The values obtained in one of the remaining patients are difficult to interpret since this patient (case 23) had received epinephrine, corticotropin and cortisone for treatment of asthma prior to quantitation of her blood. Adrenocorticotropic hormone and cortisone have been reported to decrease the urinary excretion of epinephrine and norepinephrine[4, 5] and may possibly influence the plasma concentration of the pressor amines. Patient 1 had false positive Regitine tests perhaps because of previous sedation, and an exploratory laparotomy revealed no evidence of a pheochromocytoma in the abdomen. The relatively high percentage of epinephrine in

TABLE 2.—*Patients without Pheochromocytoma*

Pt.	Approximate blood pressure, mm. Hg	Diagnosis	Concentration, μg./liter plasma			Blood urea, mg. per 100 ml.
			Epinephrine-like substance	Epinephrine	Norepinephrine	
1	220/156	Essential hypertension	2.7			N
	198/138	Essential hypertension	3.1; 2.4			N
	142/100	Essential hypertension	0	0	0	N
2	210/150	Essential hypertension	1.3			48
3	190/120	Essential hypertension	2.8	0.6	6.9	342
4	176/126	Essential hypertension	0.6			N
5	190/100	Essential hypertension	1.3	0.3	3.2	N
6	180/105	Essential hypertension	0.4			46–56
7	174/114	Essential hypertension	1.7	0.1	5.0	N
8	170/110	Essential hypertension	0.1			42–50
9	150/90	Paroxysmal* hypertension	1.1			44
10	168/116	Renal hypertension	1.9	1.1	2.4	122
11	135/105	Renal hypertension	3.1	0.0	11.2	196
12	152/104	Pregnancy with hypertension	1.8			N
13	180/115	Cushing's with hypertension†	0.1			N
14	174/110	Cushing's with hypertension	1.2			N
15	180/82	Cushing's with hypertension	1.8	1.2	1.9	N
16	150/95	Cushing's	1.0	0.8	0.6	N
17	120/85	Cushing's‡	1.7	0.4	4.0	
18	180/110	Thyrotoxicosis with hypertension	1.3	0.1	3.7	N
19	146/60	Thyrotoxicosis	1.3	1.0	1.0	N
20	135/72	Myxedema	1.2	0.2	3.2	
21	170/110	Anxiety and vascular hyperreactor	0.7			
22	134/94	Anxiety and vascular hyperreactor	0.8			
23	124/84	Asthmatic with severe attack§	2.5	0	7.9	
	105/75	Asthmatic after improvement§	0.5			
24	130/95	Post partum	1.1	0.4	2.2	N
	114/74	Post partum	0.4			N
25	110/80	Gastric carcinoma	0.7			N

* Necropsy revealed no pheochromocytoma.

† Patient had undergone 1 adrenalectomy and subtotal adrenalectomy of the other gland, a bilateral infradiaphragmatic sympathectomy and celiac ganglionectomy.

‡ Receiving cortisone in preparation for subtotal adrenalectomy.

§ Receiving cortisone.

patients with Cushing's disease and one of the patients with thyrotoxicosis is an interesting finding which must be further investigated.

No correlation was apparent between the height of the blood pressure and the concentration of pressor amines. But it should be mentioned that some of these patients were being treated with antihypertensive drugs which possibly may decrease the plasma concentration of the pressor amines. Certainly with the use of a ganglionic blocking agent it would seem possible that the quantity of norepinephrine liberated into the blood would be decreased. However, this problem requires further investigation.

RESULTS IN PATIENTS WITH PHEOCHROMOCYTOMA

The major complaints and findings in 13 patients with pheochromocytoma are summarized in table 3. Nine of these had sustained and four had paroxysmal hypertension. There were nine men and four women in this series, with an age range of 12 to 51 years. All of these patients complained of headaches; six had visual complaints; nervousness, excessive sweating, tachycardia, palpitations, sensations of weakness, and loss of weight were not uncommon. A severe retinopathy was observed in six of the patients, and elevation of the basal metabolic rate and blood sugar was

TABLE 3.—*Major Complaints and Findings in Patients with Pheochromocytoma*

Pt.	Age, yrs., sex	Relevant past histories and major symptoms	Ophthalmoscopic findings	Laboratory data		
				BMR, %	Blood sugar mg./100 ml.	Blood urea mg./100 ml.
1-s*	38M	Exertional dyspnea 18 mo., headaches 14 mo., hypertension known 12 mo., blurred vision 6 mo.	IV†	+39		21‡
2-s	43F	For 2 yr.: Diminished vision, headaches, hypertension known, tachycardia, nervousness, weight loss	IV	+27	142§	28
3-s	39M	"Goiter" removed 8 yr. ago because of enlarged thyroid, palpitations and nervousness but BMR-6 preop. Diabetes mellitus (mod. severe) 3 yr. For 8 mo.: Headaches and hypertension known, failing vision 6 wk.	IV	+49	358 256 238	26
4-s	28M	For 3½ yr.: Diminished vision, headaches, hypertension known, "jittery" feelings, easy sweating	III	+21 +6 +6	107 109	24 38
5-s	12M	Headaches, hypertension known 5 mo., nose bleeds, easy sweating and weight loss 3 mo. One convulsion with high BP (190/150), tachycardia (172) and twitching left arm and leg 2 mo. ago	IV	+9		22
6-s	36M	Headaches 5 wk., hypertension known 2 wk.	Normal	+18	125	44 26
7-s	26M	For 5 mo.: Headaches, easy sweating, palpitations, hypertension known	IV	+13 +24	130 151	30 40
8-s	21M	Hypertension known 12 yr., cerebrovascular accident with hemiplegia and hemianopsia; pheochromocytoma and metastatic rib lesion removed 3 yr. ago. For 1½ yr.: "Weak spells," excess sweating, headaches, epigastric discomfort	II	+36 +20	111	20
9-s	39M	For 3 yr.: Epigastric pressure sensations extending to chest and throat. For 2 yr.: Episodes of headaches, shaking, pallor, slowing of pulse and hypertension known	I	+4	135	
10-p*	44M	Headaches 2 yr. Accompanied for 2–3 mo. by: sweats, palpitations, tachycardia, scotomas, nausea, vomiting, paroxysmal hypertension, weight loss. Symptoms aggravated by "desensitization" treatment with I.V. and subcutaneous histamine EEG revealed left temporal abnormality.	II		115	22
11-p	48F	For 7 yr.: Hypertensive attacks with palpitations, dyspnea, cephalgia, nausea, vomiting, pallor, easy sweating, trembling, salivation	I	+20	125	28
12-p	51F	Hypertensive attacks with headaches 4½ mo. ?Myocardial infarction 1½ yr. ago. For 4 mo.: Easy sweating, weakness, weight loss	Retinal hemorrhages ? due to malnutrition	+21	198 226	
13-p	44F	For 1 yr.: Headaches accompanied sometimes by black spots before eyes, unsteady gait and hypertension known	Normal	+2	100	

* s = Sustained hypertension; p = Paroxysmal hypertension. † Grouping according to Keith, Wagener and Barker classification.[6] ‡ Normal blood urea range at Mayo Clinic = 10 to 40 mg. per 100 ml. blood. § Normal blood sugar range at Mayo Clinic = 80 to 120 mg. per 100 ml. blood.

TABLE 4.—*Pressor Amines in Patients with Pheochromocytoma before and after Removal of the Tumors*

Pt.	Preop. blood pressure, mm. Hg	Concentration, μg./liter plasma						Postop. blood pressure, mm. Hg.
		Preop.			Postop.			
		Epinephrinelike	Epinephrine	Norepinephrine	Epinephrinelike	Epinephrine	Norepinephrine	
1-s	250/170	4.7	0.8	12.4	1.5	0.1	4.5	185/125
2-s	240/150	17.7; 15.4			2.1			150/100
3-s	210/140	6.0	3.0	9.4	Not estimated—tumor not removed			
4-s	210/130	4.2	0.5	11.7	1.6	0.0	6.3	186/132
5-s	195/145	6.1	1.6	14.1	1.6	0.1	4.6	130/85
6-s	190/100	6.1	2.1	12.7	2.4	0.6	5.6	150/100
7-s	180/150	7.8			3.4			120/80
	168/136	11.4						
8-s*	160/130	4.9	0	14.8	3.1	0.9	7.0	166/100
9-s	148/98	Only estimated after provocative test			1.0			132/96
10-p	150/90	8.8	2.3	20.6	1.2	0.2	3.3	105/70
	134/94	10.2	2.9	23.0				
11-p		5.8			0.9	0.0	2.7	100/74
12-p	128/90	2.4; 2.6 (A)			0.0	0.0	0.0	105/70
13-p	120/80	1.7	0.5	3.7	0.8	0.1	2.1	130/75

* Receiving cortisone. (A) Arterial plasma.

frequently noted, but none of these patients in whom the blood urea was determined had azotemia. The results of pharmacologic tests for pheochromocytoma (histamine or Regitine or both) were positive in all 13 patients.

In table 4 and figure 1 are recorded the preoperative and postoperative (at least three days after all pressor amine medication for blood pressure stabilization had been discontinued) plasma concentrations of epinephrinelike substance, epinephrine and norepinephrine in the patients with pheochromocytoma. In the group with sustained hypertension and in two of the patients with paroxysmal hypertension, the amounts of epinephrinelike substance and the sums of epinephrine and norepinephrine were invariably greater than the highest values obtained on normal subjects or patients without pheochromocytoma. The lowest value in patients with pheochromocytoma and sustained hypertension was 4.2 μg. per liter of epinephrinelike substance and 12.2 μg. per liter for the sum of epinephrine and norepinephrine. Also, if patients with azotemia are excluded, the norepinephrine concentration in the patients with sustained hypertension and pheochromocytoma was higher than in normal subjects or patients without pheochromocytoma. In two of the patients with paroxysmal hypertension the preoperative concentrations of pressor amines were not elevated, but the blood pressures were normal when blood samples were obtained. In two of the patients following removal of the tumors the concentrations of epinephrinelike substance were slightly higher than in any of the normal subjects or patients without pheochromocytomas. One of these patients (case 8-s) had metastatic pheochromocytoma and had also received cortisone just prior to operation, which may have influenced the pressor amine concentrations. When the latter patient was seen one year later, the concentrations of epinephrinelike substance and norepinephrine were elevated (4.5 and 14.6 μg. per liter, respectively), and, though the pharmacologic tests for pheochromocytoma were equivocal, this patient very probably has residual functioning tumor tissue.

EFFECT OF PHARMACOLOGIC TESTS

In table 5 are recorded the effects of several drugs on the blood pressure and plasma con-

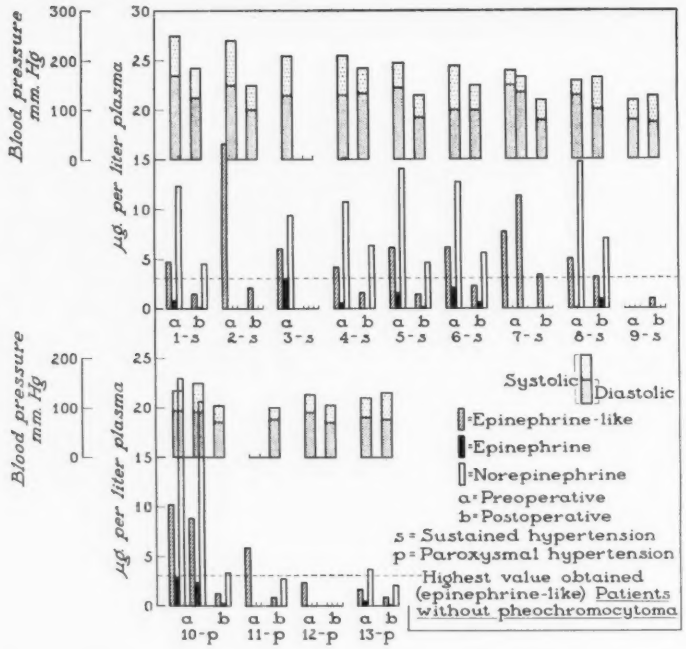

FIG. 1. Pressor amines in patients with pheochromocytoma before and after removal of the tumors.

TABLE 5.—*Effect of Pharmacologic Tests on Pressor Amines in Patients with and without Pheochromocytoma*

Pt.	Drug used	Concentration, μg./liter plasma			
		Before drug given		After drug given	
		Approximate blood pressure, mm. Hg	Epinephrinelike substance	Approximate blood pressure, mm. Hg	Epinephrine-like substance
7-s	Regitine + benodaine I.V.	180/150	7.8	144/110*	7.1
	Regitine I.V.	168/136	11.4	146/120	9.9
9-s	Histamine + Regitine I.V.	148/98	Not estimated	194/124	4.7
				144/98	6.0†
10-p	Histamine + Regitine I.V.	134/94	10.2	244/164‡	19.7
6-s	Histamine I.V.	190/100	6.1	240/138	8.1
12-p	Histamine I.V.	128/90	2.4; 2.6 (A)	250/160	11.9
Control	Histamine I.V.	174/114	1.7	184/118	0.7
Control	Histamine I.V.	114/74	0.4	112/72	0.6
Control	Histamine I.V.	170/110	0.7	210/110	2.1
Control	Histamine I.V.	134/94	0.8	178/118	1.4
9-s	1 yr. postop. histamine I.V.	130/90	0.9	148/110	1.6
Control	Regitine I.V. (previous sedation)	220/156	2.7	144/124	3.7

* Blood pressure response to drugs—actually blood pressure was 170/136 when blood sample was obtained.

† Estimated 30 minutes after above sample.

‡ Blood pressure response to histamine—actually blood pressure was 114/74 when blood sample was obtained after regitine.

(A) Arterial plasma.

centration of pressor amines in five patients with pheochromocytoma and five patients (controls) without pheochromocytoma. In patients 6-s, 10-p and 12-p, histamine intravenously administered caused a rise in blood pressure and an increase in concentration of epinephrinelike substance in plasma obtained several minutes after administration of the drug. In patient 9-s, estimation of the concentration before administration of drugs was unfortunately not performed. However, several minutes after histamine (and Regitine to depress the marked rise in blood pressure) had been given intravenously, the concentration of epinephrinelike substance was 4.7 μg. per liter. Also about ½ hour later the concentration was 6.0 μg. per liter though the blood pressure was 144 mm. Hg systolic and 98 diastolic when the blood for this second determination was obtained. This latter finding and the fact that in patient 7-s Regitine alone and Regitine followed by Benodaine intravenously administered caused no appreciable changes in the pressor amine concentrations, despite a lowering of the blood pressure, supports the view that neither of these two drugs destroys the pressor amines. No significant increase in the epinephrinelike concentration was noted following the intravenous administration of histamine to patients without pheochromocytoma or to patient 9-s when he returned about one year after operation with symptoms slightly suggestive of a recurrent pheochromocytoma. The reason for the slight increase in quantity of epinephrinelike substance in one of the control patients with hypertension from 2.7 to 3.7 μg. per liter following intravenous administration of Regitine is not known. In high concentration, Regitine will produce fluorescence detectable by the method used for determination of the pressor amines but not at the concentrations found in plasma, even after very large amounts have been administered intravenously.

Effect of Anesthesia

The effects of anesthesia on blood pressure and pressor amine concentrations in five

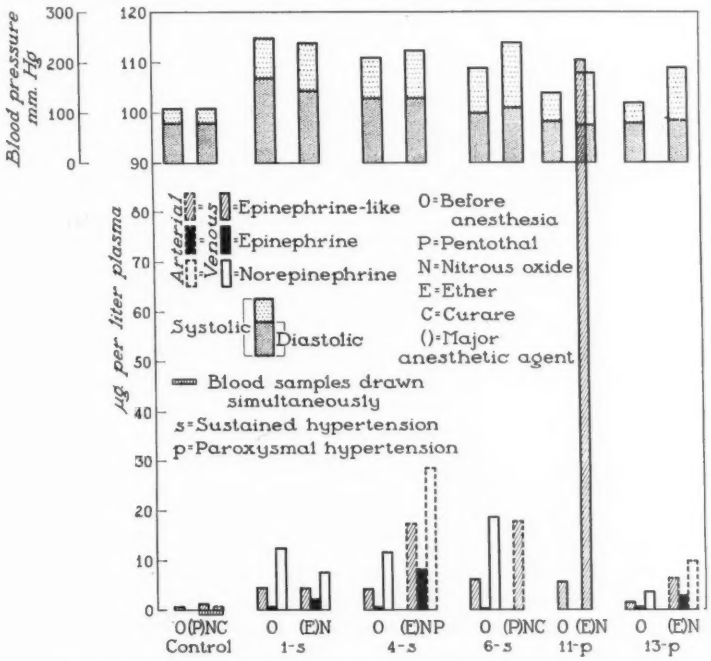

Fig. 2. The effect of anesthesia on patients with pheochromocytomas.

patients with pheochromocytoma and one patient without pheochromocytoma are represented in figure 2. It should be noted that in patients 4-s, 6-s and 13-p the arterial plasma and not the venous plasma was analyzed during anesthesia, which does not permit a strict comparison with the preanesthetic venous concentrations. In all the patients with pheochromocytoma except 1-s, the pressor amines during anesthesia were significantly increased, and markedly so in patient 11-p. In the control patient no appreciable change was observed in venous or arterial plasma drawn simultaneously during anesthesia.

Effect of Anesthesia and Palpation of Pheochromocytoma

The effect of anesthesia and anesthesia plus palpation of the pheochromocytoma in three patients is represented in figure 3 and also the effect of anesthesia and anesthesia plus palpation of the adrenal glands in a patient in whom no tumor was found. In patient 3-s the increase in concentration of epinephrinelike substance from the effect of anesthesia alone is noted and then the very marked increase after palpation of the tumor. In the latter instance concentrations were determined on plasma obtained simultaneously from venous and arterial blood of the same arm. It is interesting that the arterial sample contained more than twice the concentration in the venous plasma, indicating a considerable loss of pressor amines in the forearm secondary to metabolic destruction or diffusion or both. This patient had a malignant pheochromocytoma with extensive metastases which were not removed. In patient 12-p there was no effect of anesthesia on either the venous or arterial pressor amine concentrations. However, palpation of the tumor caused a considerable increase in the arterial concentration. Only a slight increase in concentration was noted in the patient without a pheochromocytoma during anesthesia and adrenal gland palpation.

No correlation is apparent between the type of anesthetic agents employed and the quantity of pressor amines liberated into the circula-

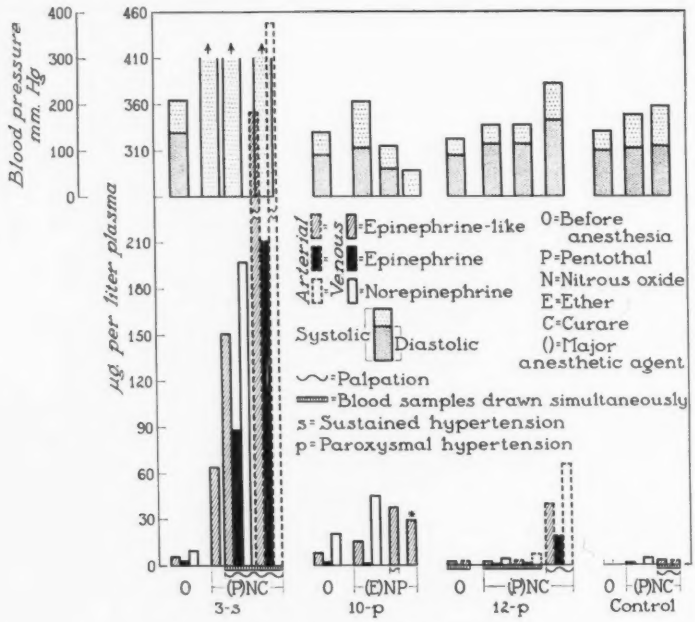

Fig. 3. The effect of anesthesia and operative manipulation on patients with pheochromocytomas.

ion in these patients with pheochromocytoma. However, the series is too small to permit any definite conclusions. Neither Pentothal sodium nor ether produced any fluorescence with our analytic procedure.

Results of Pheochromocytomas Analyzed

Finally, alcoholic extracts of the pheochromocytomas removed at operation were prepared in the following manner as suggested by Dr. E. C. Kendall:

As soon as each tumor was removed it was placed in dry ice and frozen solid to minimize oxidation and deterioration of the pressor amines. Five to 10 Gm. samples of the frozen tumor were crushed, weighed and extracted with 5 volumes of cold alcohol containing a small amount of acetic acid and sodium bisulfite.

These extracts were then diluted 5,000 to 10,000 times with glass-distilled water, and 10 ml. of this dilution was condensed directly with ethylene diamine without initial adsorption on an alumina column as is necessary with blood. This was deemed advisable since the percentage loss of pressor amines from these alcoholic extracts during the adsorption, and elution process, despite the addition of sodium thiosulfate as an antioxidant, is considerable. A poor recovery is also noted if water solutions of epinephrine and norepinephrine with this antioxidant are passed through an alumina column. With addition of water solutions of pressor amines or tumor extracts to a mixture of plasma, antioxidant (sodium thiosulfate) and anticoagulant (sodium fluoride) the recovery of epinephrine or norepinephrine or both is approximately 93 per cent. Thirteen experiments to determine the recovery percentage were performed on specimens of plasma to which various quantities of epinephrine or norepinephrine or both had been added. These were then analyzed according to the method of Weil-Malherbe and Bone.[1] The mean recovery was 92.9 per cent, and the standard deviation of the recovery percentages was 4.7 per cent. The latter adds to the error of 14 per cent previously reported[2] when quantitation of epinephrine and norepinephrine is made using aqueous mixtures with and without sodium thiosulfate. Considering the errors as independent, the total error measured as standard deviation is about 15 per cent ($\sqrt{14^2 + 4.7^2}$).

Table 6.—*Pheochromocytomas*

Pt.	Site	Wt., Gm.	Mg./Gm. tumor			
				Epinephrine-like	Epinephrine	Norepinephrine
1-s	L. ad.*	25		1.73	1.21	1.64
2-s	L. ad.*	165	I	0.38	0.04	1.07
			II	0.29	0.02	0.85
4-s	R. ad.†	16		0.36	0.20	0.50
5-s	L. ad.*	20		1.08	0.02	3.34
6-s	Liver hilus	32		0.56	0.1	1.45
7-s	L. ad.*	70	I	0.06		
			II	0.27		
8-s	Periaortic	25		0.52	0	1.6
9-s	R. ad.†	120	I	4.5		
			II	5.78		
10-p	R. ad.†	25		1.78	0.76	3.22
11-p	R. ad.†	45		5.87	4.49	4.37
12-p	L. ad.*	200	I	0.38	0.20	0.57
			II	0.70	0.46	0.76
13-p	L. ad.*	17.2		3.30	1.59	5.40

Note: Tumor not removed from patient 3-s.
* Region of left adrenal gland.
† Region of right adrenal gland.

Extraneous fluorescence from substances other than epinephrine and norepinephrine in these diluted extracts is negligible. Consequently, quantitation of the epinephrine and norepinephrine in these tumor extracts was accomplished in about two hours, whereas the analysis of plasma required about four and one-half hours. A number of tumor or plasma extracts may be analyzed simultaneously without requiring much additional time. If kept in the refrigerator, the alcoholic tumor extracts did not appreciably deteriorate for at least several weeks (one sample showed no change in the pressor amine concentrations after 27 days).

The locations, weights and concentrations expressed in milligrams of pressor amines per gram of tumor are recorded in table 6.

In all of the tumors analyzed for epinephrine and norepinephrine, the amount of norepinephrine was greater than that of epinephrine except in patient 11-p, in whom the per-

centages were about equal. Two extracts were prepared from different portions of four of the tumors, and the difference of pressor amine concentrations is particularly noticeable in patients 7-s and 12-p. This latter finding indicates that the concentrations are not uniform in some pheochromocytomas. In addition to the more accurate fluorometric quantitation of pressor amines in the tumor extracts, estimations were also made by the method of paper chromatography.[7] Similar values obtained by the two methods lend further support to the specificity of the fluorometric method. Recently in one pheochromocytoma discovered at necropsy, hydroxytyramine in addition to epinephrine and norepinephrine was found on chromatographic analysis. Addition of known hydroxytyramine to the sample intensified this spot when the chromatograms were run in two different solvents (75 per cent phenol; normal butanol saturated with 1 normal hydrochloric acid). It is possible that the appearance of hydroxytyramine was in some way related to postmortem changes in the embalmed specimen. This is the first time that we have observed any catechols other than epinephrine and norepinephrine in 35 pheochromocytomas analyzed chromatographically. Hydroxytyramine has been found in sheep adrenals[8] and human urine.[9]

COMMENT

Of the 13 patients with pheochromocytoma reported, all those with sustained hypertension and two with paroxysmal hypertension had elevated plasma concentrations of pressor amines as compared with normal subjects and patients with hypertension due to other causes. Of the two remaining patients with paroxysmal hypertension and pheochromocytoma, the concentration of pressor amines became elevated in one after a provocative histamine test and in the other during anesthesia administration—which often simulates a provocative test in patients with pheochromocytoma. Unfortunately the effect of histamine was not observed in this latter patient. In this series and method of analysis, plasma concentrations greater than 4 μg. per liter of epinephrinelike substance and 12 μg. per liter for the sum of epinephrine and norepinephrine have without exception been diagnostic for pheochromocytoma. However, since our series is small, patients with azotemia should be more carefully evaluated, since in this instance there may be retention of fluorescent substances other than epinephrine and norepinephrine which would falsely give high values for the pressor amine concentration. The possibility of the retained fluorescent substance being phenol has been fairly well excluded by treating ethylenediamine with concentrations of phenol which may occur with severe azotemia. No fluorescence was obtained.

It was found essential to obtain blood during or shortly after a paroxysm of hypertension—either naturally occurring or induced by a drug such as histamine—to establish a diagnosis in some of the patients with paroxysmal hypertension secondary to pheochromocytoma. In this series of 13 patients the per cent of norepinephrine in the preoperative and postoperative plasma was invariably higher than that of the epinephrine. This latter finding is consistent with the higher concentrations of norepinephrine noted in the tumor extracts and in the plasma of normal subjects. In patient 9-s, chromatographic separation of pressor amines in the tumor extract revealed 5 mg. per gram tumor of epinephrine and 1.3 mg. per gram tumor of norepinephrine. Very likely the plasma concentrations in this patient would have also contained a high percentage of epinephrine, but unfortunately the method[2] for determination of the individual pressor amines was not available.

Using an entirely different fluorometric method of analysis,[10] Lund reported data on five patients in whom the total amounts of epinephrine and norepinephrine in plasma were elevated during episodes of paroxysmal hypertension.[11] Four of these patients were proved to have pheochromocytomas, but no tumor was found in the fifth patient. Von Euler, Lund and co-workers,[12] using Lund's method, also reported the total plasma concentrations of epinephrine and norepinephrine in a patient with pheochromocytoma. These investigators

were unable to estimate the concentrations of pressor amines in the plasma of normal subjects.

Summary

The results of quantitation of epinephrine and norepinephrine in the plasma and tumor extracts of 13 patients with pheochromocytoma and in the plasma of small groups of normal subjects and patients with hypertension and various diseases unassociated with pheochromocytoma are reported. The preoperative plasma concentrations of epinephrinelike substance and total epinephrine and norepinephrine in all the patients with sustained hypertension and pheochromocytoma were significantly elevated (more than 4 μg. per liter of plasma of epinephrinelike substance and more than 12 μg. per liter of plasma for the sum of epinephrine and norepinephrine). Though only two of the four patients with paroxysmal hypertension secondary to pheochromocytoma had an elevated concentration of pressor amines, these concentrations could be significantly increased with a provocative drug (for example, histamine) in patients with pheochromocytoma but not in patients without such a tumor.

It appears thus far in this investigation that chemical estimation of the pressor amines in plasma—if combined with provocative tests in patients with the paroxysmal type of hypertension—is a valuable test for screening patients suspected of having pheochromocytoma. Except in patients with pheochromocytoma, the magnitude of hypertension appears to bear no relation to the level of pressor amines in the plasma.

Attention is also called to the occurrence of epinephrine-norepinephrine release in large amounts in most of these patients during anesthesia and especially after palpation of the pheochromocytomas.

Sumario Español

Se informan los resultados de la determinación de epinefrina y norepinefrina en el plasma y en los extractos de tumores en 13 pacientes con feocromocitoma y en el plasma de un pequeño grupo de sujetos normales y en pacientes con hipertensión y varias otras enfermedades no asociadas con feocromocitoma. Las concentraciones plasmáticas preoperatorias de substancias similares a la epinefrina y el total de epinefrina y norepinefrina en todos los pacientes con hipertensión sostenida y feocromocitoma estuvieron significativamente elevadas (más de 4 microgramos por litro de plasma de substancias similares a epinefrina y más de 12 microgramos por litro de plasma de la suma de epinefrina y norepinefrina). Aunque solamente dos de cuatro pacientes con hipertensión paroxística secundaria a feocromocitoma tuvieron una concentración elevada de aminas presoras, estas concentraciones pudieron ser significativamente aumentadas con droga provocativa (por ejemplo, histamina) en pacientes con feocromocitoma pero no en pacientes sin tal tumor.

Aparentemente en esta investigación la estimación química de las aminas presoras del plasma—si combinada con pruebas provocativas en pacientes con el tipo paroxístico de hipertensión—es una prueba valiosa para encubrir pacientes sospechados de tener feocromocitoma. Excepto en pacientes con feocromocitoma, la magnitud de la hipertensión parece no tener relacción al nivel de aminas presoras en el plasma.

También se llama la atención a la posibilidad de liberación en grandes cantidades de epinefrina y norepinefrina en muchos de estos pacientes durante la anestesia y especialmente luego de la palpación del feocromocitoma.

Acknowledgment

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REFERENCES

[1] Weil-Malherbe, H., and Bone, A. D.: The chemical estimation of adrenaline-like substances in blood. Biochem. J. **51:** 311, 1952.

[2] Manger, W. M., Baldes, E. J., Flock, E. V., Bollman, J. L., Berkson, J., and Jacobs, M.: A method for quantitative estimation of epinephrine and norepinephrine: Preliminary report. Proc. Staff Meet., Mayo Clin. **28:** 526, 1953.

[3] Weil-Malherbe, H., and Bone, A. D.: The

adrenergic amines of human blood. Lancet **1:** 974, 1953.

[4] VON EULER, U. S., AND LUFT, R.: The effect of adrenocorticotrophic hormone (ACTH) and adrenocorticotrophically active peptides (ACTH peptides) on the circulating eosinophils and urinary excretion of adrenaline and noradrenaline in a human subject. Acta Endocrinol. **3:** 323, 1949.

[5] LUFT, R., AND VON EULER, U. S.: Excretion of catechol amines during administration of ACTH, cortisone and desoxycorticosterone acetate. Metabolism **1:** 179, 1952.

[6] KEITH, N. M., WAGENER, H. P., AND BARKER, N. W.: Some different types of essential hypertension: Their course and prognosis. Am. J. M. Sc. **197:** 332, 1939.

[7] ROTH, G. M., AND FLOCK, E. V.: Unpublished data.

[8] GOODALL, McC.: Dihydroxyphenylalanine and hydroxytyramine in mammalian suprarenals. Acta chem. scandinav. **4:** 550, 1950.

[9] VON EULER, U. S., HAMBERG, U., AND HELLNER, S.: β-(3:4-Dihydroxyphenyl)ethylamine (hydroxytyramine) in normal human urine. Biochem. J. **49:** 655, 1951.

[10] LUND, A.: Simultaneous fluorimetric determinations of adrenaline and noradrenaline in blood. Acta pharmacol. et toxicol. **6:** 137, 1950.

[11] LUND, A.: Adrenaline and noradrenaline in blood and urine in cases of pheochromocytoma. Scandinav. J. Clin. & Lab. Investigation. **4:** 263, 1952.

[12] VON EULER, U. S., LUND, A., OLSSON, A., AND SANDBLOM, P.: Noradrenaline and adrenaline in blood and urine in a case of phaeochromocytoma. Scandinav. J. Clin. & Lab. Investigation **5:** 122, 1953.

Hemodynamic Studies in Sickle Cell Anemia

By LEONARD LEIGHT, M.D., THOMAS H. SNIDER, M.D., GEORGE O. CLIFFORD, M.D., AND HARPER K. HELLEMS, M.D.

Hemodynamic studies in 13 unselected patients with sickle cell anemia are reported. Twelve of these patients were also studied during mild exercise. The cardiac output at rest was elevated in all and rose significantly with exercise in 9 of the 12 patients. The importance of the increased percentage extraction of oxygen by the tissues in modifying the response of the cardiac output is discussed. The similarity of the response to exercise in the majority of these chronically anemic patients compared with the normal response is described. Included in this series is one case with secondary cor pulmonale and one case of concurrent rheumatic heart disease.

THE clinical mimicry of rheumatic fever and rheumatic heart disease by sickle cell anemia, and the difficulty in differentiating some of the manifestations of sickle cell anemia from these conditions has been noted many times in the literature. Although rheumatic heart disease has been stated to be a rare concomitant of sickle cell disease,[1] their occurrence together has been described.[2, 3] Sickle cell anemia as a cause of pulmonary vascular occlusion, pulmonary hypertension, and subsequent right ventricular hypertrophy is now well authenticated.[4] It has been suggested that sickle cell thrombi in the coronary vasculature occasionally result in coronary insufficiency.[5]

In view of the varied pathologic findings and the puzzling clinical picture presented by patients with sickle cell anemia, it was felt that hemodynamic studies in a group of such patients would be of interest. Furthermore, these patients offered a unique opportunity to study the circulatory adjustments to chronic and relatively constant anemia. Although studies of the circulatory state in anemia have been reported,[6, 7] the response of such patients to exercise has not been noted. As in other disease states affecting the cardiovascular system, knowledge of the behavior of patients during activity is essential to a more complete understanding of the circulatory state.

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METHODS

All patients were studied in the fasting state, without sedation. Venous catheterization was performed in the usual fashion. When possible, a double lumen catheter was employed, the distal lumen being wedged in a branch of the pulmonary artery to obtain "pulmonary capillary" pressure.[8] A 20-gauge needle was inserted into the brachial artery to obtain arterial blood and pressure. Cardiac output, utilizing the Fick principle, was obtained at rest, expired air for oxygen consumption being collected for three minutes in a Tissot Spirometer. Immediately upon conclusion of the determination of cardiac output, simultaneous pulmonary artery, pulmonary capillary, and brachial artery pressures were measured. The patients then exercised in the recumbent position by pedaling a bicycle at the rate of 50 to 60 revolutions per minute for three to four minutes. Simultaneous pressures in the pulmonary artery, pulmonary capillary, and brachial artery were recorded during the exercise period. Expired air for oxygen consumption was collected over the last half minute of exercise, and blood was drawn simultaneously from the pulmonary artery and brachial artery at as constant a rate as possible during the entire period of air collection. Although it is recognized that a steady state may not be present under the conditions of such an exercise period,[9] it is believed that an average cardiac output is obtained.[10] After a period of rest, usually 10 to 15 minutes, the catheter was withdrawn and right ventricular and auricular pressures recorded.

Pressures were obtained with Sanborn Electromanometers, and recorded on a Sanborn Polyviso instrument. The zero point for all pressures was 10 cm. anterior to the back. Mean pressures were obtained by electrical integration. Blood samples were analyzed for oxygen content by the method of Van Slyke and Neil,[11] duplicate samples being required to

check within 0.1 volumes per cent. Oxygen in expired air was measured by means of a Pauling Oxygen Analyzer using a correction factor of 1.007 to convert expired volume to inspired volume.[12]

The per cent oxygen utilized by the tissues expressed in terms of the arterial oxygen content was calculated as follows:

$$\%\ \textit{oxygen utilized} = \frac{\textit{A-V oxygen difference cc./L.}}{\textit{Arterial oxygen content cc./L.}} \times 100$$

The oxygen transport to the tissues[23] was expressed as follows:

Oxygen transport (cc./min.) = Cardiac output (L/min.) × Arterial oxygen content (cc./L.)

Pulmonary arteriolar resistance and total peripheral resistance were expressed[18] in dynes seconds cm^{-5}. Left ventricular work against pressure was calculated as the product of mean brachial artery pressure and cardiac output and expressed in kilogram-meters per minute.[13]

Case Material

Twelve patients were studied by means of cardiac catheterization both at rest and during exercise, while one patient (L.W.) was studied only during the resting state. The patients varied in age from 12 to 39 years, and had hemoglobins varying from 5.8 to 10.8 Gm. per 100 cc. (table 1). Patient J.P., who had a hemoglobin level of 10.8 Gm. per 100 cc., received 500 cc. blood the day prior to study. No other patient had received a blood transfusion for at least several weeks prior to catheterization. Cardiac hypertrophy and/or dilatation was demonstrable by means of electrocardiograms or x-ray films in all patients. Left auricular enlargement was fluoroscopically visualized in four, being of slight degree in three, and moderate degree in one. The electrocardio-

Table 1.—*Summary of Hemodynamic Findings in 13 Patients with Sickle Cell Anemia*

Pt.	Age	Hemoglobin Gm. %	State	Ventilation L./min.	O_2 Consumption cc./min./M.²	A-V O_2 Difference cc./L.	Cardiac Output L./min.	Cardiac Index L./min./M².	Mean Pressures mm. Hg				Resistances dynes sec. cm.$^{-5}$		Work of Left Ventricle Kg.-meters/min.	Arterial O_2 Saturation %
									Brachial Artery	Pulmonary Artery	Pulmonary Capillary	Right Auricle	Pulmonary Arteriolar	Total Peripheral		
D.H.	12	9.7	Rest	7.1	164	29.3	6.5	5.4	75	28	23	−1	62	844	6.9	97.4
			Exercise	9.1	243	38.4	7.6	6.3	80	37				700	9.9	98.0
B.A.	39	7.7	Rest	7.6	175	28.5	10.2	6.2	77	31	7	1	188	603	10.7	82.9
			Exercise	13.6	276	30.1	15.1	9.2		44	10		204			88.6
J.P.	27	10.8	Rest	6.6	147	27.3	9.3	5.4	82	20	14	3	52	704	10.4	86.9
			Exercise	14.0	291	34.1	14.7	8.5	88	26	17		49	478	17.7	86.2
E.F.	20	6.0	Rest	5.2	122	19.2	8.9	6.4	97	20	14	5	54	871	11.7	89.3
			Exercise	8.3	194	23.3	11.7	8.4		21	14		48			90.9
P.B.	19	5.8	Rest	5.3	136	26.5	6.9	5.1	76	17	13	7	46	880	7.1	88.5
			Exercise	12.3	255	26.5	12.9	9.6	92	28	24		25	570	16.1	79.1
C.H.	13	6.7	Rest	6.3	168	28.5	7.1	5.9	87	11	8	2	34	979	8.4	91.1
			Exercise	10.4	285	34.8	9.8	8.2	83	19	13		49	677	11.1	95.2
S.T.	17	8.3	Rest	8.3	157	21.0	14.5	7.5	98	17	13	7	22	540	19.3	97.5
			Exercise	10.5	220	31.5	13.6	7.0	98	19	10		53	576	18.1	99.7
I.E.	37	8.6	Rest	15.7	187	30.4	10.3	6.1	90	17	9	4	62	698	12.6	93.4
			Exercise	31.4	304	41.5	12.3	7.3	115	18	9		58	747	19.2	95.9
B.G.	15	7.7	Rest	14.4	307	19.4	19.2	15.9	80	18	11	3	29	333	20.9	96.1
			Exercise	9.7	284	27.7	12.4	10.2	90	16	9		45	580	15.2	93.9
O.B.	25	8.4	Rest	6.3	129	22.1	9.2	5.8	84	17	12	5	43	730	10.5	92.1
			Exercise	10.1	197	31.9	9.7	6.1	82	23	15		66	676	10.8	92.9
L.W.	25	9.3	Rest	7.0	144	24.3	10.1	5.9	80	15	9		47	633	11.0	94.2
			Exercise													
L.S.	19	7.0	Rest	7.8	161	21.5	10.6	7.5	80	15	10	4	38	603	11.5	89.4
			Exercise	12.9	269	26.9	14.1	10.0	80	18	10		45	468	15.3	87.8
M.S.	18	6.1	Rest	6.1	121	22.1	8.5	5.5	78	20	15	10	47	733	9.1	93.4
			Exercise	8.8	219	24.8	13.6	8.8	88	15	12		18	517	16.3	90.9
Averages	22	7.9	Rest	8.0	163	24.6	10.1	6.8					56	704	11.4	91.7
			Exercise	12.6	250	30.9	12.3	8.3					60	599	15.0	91.6

TABLE 2.—*Summary of Electrocardiographic Findings*

Abnormality	No.
None	6
1st Degree Heart Block	1
Incomplete RBBB*	1
Left Ventric. Hypertrophy	4
Left Auric. Enlarg.	1
Nonspecific Changes	1

* Right bundle-branch block.

graphic findings in this group of cases are shown in table 2. All patients had systolic murmurs, and three had apical diastolic murmurs. One patient (B.A.) entered the hospital in congestive failure, but was compensated at the time of study. None of the other patients had ever been in clinical cardiac failure.

The subjects were unselected. Catheterization was performed as each was brought to our attention, unless there was specific contraindication or consent was not forthcoming. All fulfilled the usual laboratory and clinical criteria for sickle cell anemia, all but one having been referred from the Hematology Clinic. Electrophoretic studies* of the hemoglobin were available in seven cases, and, when obtained, indicated that those patients were suffering from true sickle cell anemia.[14]

RESULTS

The more important data obtained in the study of this group of subjects is tabulated in table 1. Cardiac index was elevated at rest in all patients, ranging from 5.1 to 15.9 liters per minute per square meter of body surface area. Patient B.G., who had a resting cardiac index of 15.9 L. per minute per square meter of surface area, was not in a basal state, since the cardiac index fell with exercise to 10.2 L. per minute per square meter accompanied by a fall in oxygen consumption from 307 to 284 cc. per minute per square meter, a decrease in ventilation from 14.4 to 9.7 L. per minute and no significant change in pulmonary pressures. Excluding this patient, the resting cardiac index ranged from 5.1 to 7.9 L. per minute per square meter, and averaged 6.1 L. per minute per square meter. All patients but one (again excluding B.G.) augmented the cardiac index with exercise (fig. 1). The exercising cardiac index ranged from 6.1 to 10.0 L. per minute per square meter and averaged 8.1 L. per minute per square meter.

The oxygen consumption at rest for the group as a whole averaged 163 cc. per minute per square meter, varying from 121 to 307 cc. Excluding patient B.G., who had a resting oxygen consumption of 307 cc. per minute per square meter, the mean resting oxygen consumption was 154 cc. per minute per square meter, and varied from 121 to 187 cc. These findings are comparable to those of Brannon and co-workers[7] and Stewart and associates[25] who found mean resting oxygen consumptions of 146 and 143 cc. per minute per square meter, respectively, for resting patients with less than 11 Gm. hemoglobin per 100 cc. In a group of normal subjects, Dexter and his colleagues[18] found a mean resting oxygen consumption of 145 cc. per minute per square meter with a range of 127 to 168 cc.

In this series, there is no relation between the level of hemoglobin and the resting oxygen consumption. Our findings are, on the whole, in agreement with those of others who have found the basal metabolic rate to be normal or slightly elevated in anemia.[22] The mean oxygen consumption during exercise was 250 cc. per minute per square meter, indicating a mild degree of work.

The arterial oxygen saturation at rest for the whole group averaged 91.7 per cent, and in 9 of 13 patients, was below 94 per cent. For the 12 exercised patients, the mean arterial oxygen saturation was 91.6 per cent. Five of

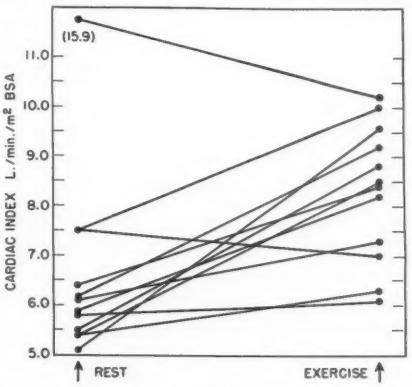

FIG. 1. Changes in cardiac output with exercise.

* Electrophoretic studies were carried out by Dr. Harvey Itano, California Institute of Technology.

the 12 patients experienced a fall in arterial oxygen saturation during exercise. Among the nine individuals who had a resting saturation below 94 per cent, seven failed to raise the saturation above 94 per cent during exercise.

The work of the left ventricle against pressure exceeded 9 kilogram-meters per minute in 9 of the 13 patients at rest, averaging 11.4 kilogram-meters per minute for the whole group. In those patients in whom it was measured during exercise, the average left ventricular work rose to 15.0 kilogram-meters per minute.

Despite the presence of clinical, electrocardiographic, and/or radiologic findings compatible with organic heart disease in all of these patients, the resting pulmonary pressures were normal in all but two. One patient (B.A.), the oldest individual in this group, who had entered the hospital in congestive failure, demonstrated the hemodynamic pattern of cor pulmonale. This patient had no symptoms or signs of primary pulmonary disease. At rest, his pulmonary artery pressure was 46/22 mm. Hg with a mean pressure of 31 mm. Hg, and pulmonary capillary mean pressure of 7 mm. Hg. The corresponding mean pressures during exercise were 44 and 10 mm. Hg. The pulmonary arteriolar resistance at rest was 188 dynes second cm.$^{-5}$, showing no significant rise with exercise. At the time of catheterization, the patient was clinically free of signs of heart failure. The resting right auricular mean pressure was 1 mm. Hg. This patient appears to represent an example of cor pulmonale secondary to pulmonary vascular disease produced by sickle cell thrombi.[4]

One of the series (D.H.) demonstrated hemodynamic and clinical findings consistent with the diagnosis of concurrent sickle cell anemia and rheumatic heart disease. This individual was a 12 year old girl with a prior history of several bouts of migratory polyarthritis. She had a harsh, grade IV, apical systolic murmur and an intermittently heard rumbling apical diastolic murmur. Cardiac enlargement was demonstrated by x-ray films, left ventricular hypertrophy by electrocardiograms, and left auricular enlargement out of proportion to the generalized cardiac dilatation by fluoroscopy. At rest, the mean pulmonary capillary pressure was 23 mm. Hg, and the pulmonary artery pressure was 37/18 mm. Hg, with a mean of 28 mm. Hg. During exercise, the pulmonary artery pressure rose to 50/22 mm. Hg, with a mean of 37 mm. Hg. Pulmonary capillary pressure was not obtained during exercise. Some four months after cardiac catheterization, the patient reentered the hospital febrile, with acute inflammatory polyarthritis, elevated sedimentation rate, and cardiac dilatation on x-ray films of a greater degree than previously noted. A subcutaneous nodule was palpable at this time on the extensor surface of her left arm immediately distal to the elbow. During her stay in the hospital, the patient experienced an episode of severe left ventricular failure. The subcutaneous nodule, which gradually regressed over a period of several days, was considered classic for rheumatic fever.

Four other patients (J.P., P.B., C.H., O.B.), who had normal resting pressures, experienced a rise in pulmonary artery pressure with exercise, the pulmonary artery pressure reaching abnormal levels in three, and increasing from a mean of 11 to 19 mm. Hg in the other patient (C.H.) (table 1). In three of these patients, this was accompanied by a slight rise in pulmonary capillary pressure, a tendency for the pulmonary artery–pulmonary capillary gradient to widen, and no significant change in pulmonary arteriolar resistance. These changes are probably related to the increased pulmonary blood flow with exercise as described in normal subjects,[12] though, in this series, there was no correlation between the increment in cardiac index incident to exercise and change in pulmonary pressures. The fourth patient (P.B.), whose mean pulmonary artery pressure rose from 17 to 28 mm. Hg with exercise, had a corresponding increase in mean pulmonary capillary pressure from 13 to 24 mm. Hg, no change in pulmonary artery–pulmonary capillary gradient, and no significant change in pulmonary arteriolar resistance. This patient had the usual sickle cell history of bouts of polyarthritis in childhood. An apical diastolic murmur and a grade I apical systolic murmur were heard on auscultation. Cardiac enlarge-

ment and prominent pulmonary artery segment were present radiographically. However, no left auricular enlargement could be demonstrated. In view of the absence of auricular enlargement, mitral stenosis seems unlikely. The increase in pulmonary pressures during exercise in this case may well have been a manifestation of high output left ventricular failure.

Discussion

All but one of the patients in this series had murmurs which were apparently of functional origin, such as have been previously described in sickle cell anemia and other types of anemia.[1, 15, 16] Within the range of hemoglobins in this group, there did not appear to be a correlation between the degree of anemia and the intensity, type, or location of the various murmurs noted.

Cardiac catheterization disclosed complicating organic heart disease in two patients in this series. One of the patients presented the pattern of cor pulmonale which, since the pathologic studies of Yater,[4] has been accepted as one of the complications of sickle cell anemia. In the absence of cardiac catheterization, this diagnosis is difficult to make, since the clinical spectrum which may be found in patients with cor pulmonale complicating sickle cell anemia may be simulated entirely by the anemia, per se.

In the other case, the hemodynamic findings, coupled with the clinical findings, were indicative of mitral valvulitis. The incidence of rheumatic fever among patients with sickle cell anemia remains a subject of considerable controversy. As a result of the studies of Klinefelter[1] and others, the difficulties in clinically separating the signs and symptoms of rheumatic fever and sickle cell anemia have become widely recognized. However, such a separation is of importance in view of the therapy available for the treatment of the acute attack of rheumatic fever, and the demonstrated usefulness of prophylactic medication in preventing future attacks and some of the complications of this disease. The case here described emphasizes this point. Despite the findings of mitral valvular disease, there was reluctance to start this patient on indefinite prophylactic penicillin therapy because of the many reports indicating the infrequent concurrence of rheumatic heart disease and sickle cell anemia. The subsequent episode of acute rheumatic fever some months later might have been prevented if such prophylactic therapy had been instituted.

Porter[17] has recently suggested, on the basis of his experience with patients suffering from chronic parasitic anemia, that the cardiac output is not increased at rest in the patient with chronic, severe, and constant anemia. Our findings are not in accord with this viewpoint. The mean resting cardiac index of 6.1 L. per minute per square meter of body surface area in this group is significantly higher than the mean normal values of 3.32 to 4.2 L. per minute per square meter reported by various authors using the same technic.[12, 18-20] Our results in sickle cell anemia are comparable to those of Brannon and associates,[7] who reported a mean cardiac index of 5.7 L. per minute per square meter in a variety of anemic patients with hemoglobins of less than 10 Gm. per 100 cc.

Although the cardiac index was elevated at rest in all patients, the level of cardiac index bore no relation to the hemoglobin or oxygen content levels. This lack of a linear relationship between the cardiac index and the oxygen content appears to be explained by a peripheral compensatory mechanism whereby the percentage of oxygen extraction is increased as the oxygen content of the arterial blood decreases. Excluding patient B.G., the mean arteriovenous oxygen difference at rest was 25.1 cc. per liter, and the mean utilization of oxygen expressed as per cent of arterial oxygen content was 26.8 per cent (table 3). The tendency for the per cent of oxygen extracted from the arterial blood to increase as the oxygen content decreases is illustrated in figure 2 and is in agreement with the findings of Liljestrand.[21] This relationship is better demonstrated in figure 3, where the oxygen transport to the tissues is related to the percentage extraction of oxygen. It is apparent that as the quantity of oxygen delivered to the tissues per minute decreases, the percentage

TABLE 3.—*Data Relating Oxygen Content, Oxygen Transport, and Oxygen Utilization*

Patient	O_2 Content cc./L.		A-V O_2 Difference cc./L.		Cardiac Output L./min.		O_2 Transport cc./min.		O_2 Utilization in % of O_2 Content	
	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.
D. H.	125.5	125.1	29.3	38.4	6.5	7.6	816	931	23.3	30.7
B. A.	90.4	90.8	28.5	30.1	10.2	15.1	922	1371	31.5	33.1
J. P.	124.8	125.5	27.3	34.1	9.3	14.7	1161	1845	21.9	27.1
E. F.	71.2	66.7	19.2	23.3	8.9	11.7	634	780	26.9	34.9
P. B.	68.6	65.6	26.5	26.5	6.9	12.9	473	846	38.6	40.4
C. H.	80.7	84.8	28.5	34.8	7.1	9.8	573	831	35.3	41.0
S. T.	107.3	109.8	21.0	31.5	14.5	13.6	1556	1493	19.6	28.6
I. E.	107.6	108.7	30.4	41.5	10.3	12.3	925	1337	28.2	38.1
O. B.	103.3	104.0	22.1	31.9	9.2	9.7	868	1009	21.4	30.7
L. W.	116.6		24.3		10.1		1178		20.8	
L. S.	83.1	82.3	21.5	26.9	10.6	14.1	881	1160	25.8	32.6
M. S.	76.5	75.5	22.1	24.8	8.5	13.6	650	1027	28.8	32.8
Mean			25.1	31.3					26.8	33.6

extraction of oxygen from the arterial blood increases. This important compensatory phenomenon is probably due to an increased capillary diffusing surface in such patients,[21, 24] and serves partially to satisfy the needs of the tissues for sufficient oxygen in face of a lowered oxygen carrying capacity of the blood.

Despite the fact that with increasing anemia there is a tendency to extract a greater percentage of available oxygen at the periphery, this mechanism fell far short of providing the needs of the tissues for oxygen in this group. The absolute quantity of oxygen delivered to the periphery in terms of the arteriovenous

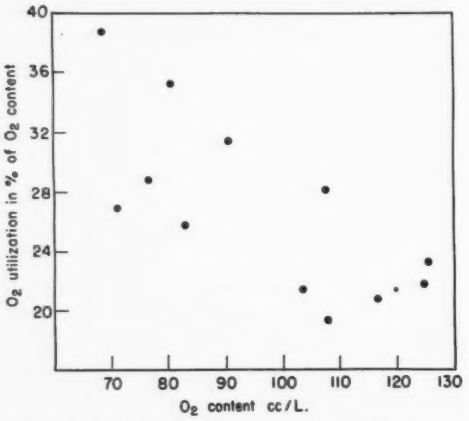

FIG. 2. Relation between arterial oxygen content and oxygen utilized by tissues, expressed as per cent of arterial oxygen content.

difference was less than in normal subjects, and the per cent utilization in terms of oxygen content less than is seen in other conditions at rest, for example, in patients with congestive failure.

As previously noted (fig. 1), all but two patients responded to exercise with an increase in cardiac index. Of the two patients who had a fall in cardiac index with exercise, one of them, patient B.G., a 15 year old boy with a hemoglobin of 7.7 Gm. per 100 cc., has been mentioned previously as not being in a basal state at rest. Nevertheless, his resting cardiac index of 15.9 L. per minute per square meter of body surface area illustrates his capacity for increasing his cardiac output to high levels. We have no explanation for the failure of the other patient (S.T.) to increase his cardiac output with exercise. Since there was no significant change in pulmonary pressures with exercise, it is not believed that this was due to cardiac failure. Patient (P.B.), who increased his cardiac index with exercise, probably suffered mild left ventricular failure during the exercise period.

The response of normal individuals to exercise shows considerable variation. According to Ferrer and associates,[9] the normal individual, when exercised, will increase his cardiac output by 600 cc. or more per 100 cc. increase in oxygen consumption. Similar data have been calculated for the entire

group and are illustrated in table 4. Of the patients who increased their cardiac output with exercise, all but one increased it by more than 600 cc. per 100 cc. increase in oxygen consumption. This includes the two individuals who are believed to have organic disease. Although the capacity to respond to exercise is, in general, restricted in patients with mitral stenosis, we have not infrequently seen a normal response to exercise of this degree in patients with mild to moderate mitral stenosis. Patients with mild cor pulmonale due to emphysema frequently have a normal response to exercise.[20]

That the response of the cardiac output to bodily needs was essentially normal is well illustrated by the results obtained with exercise. For the group, excluding patient B.G., the mean arteriovenous oxygen difference during exercise rose to 31.3 cc. per liter and the mean per cent oxygen utilization in terms of the oxygen content rose to 33.6 per cent (table 3). Using the data of Hickam[20] obtained in a group of normal individuals, the calculated mean per cent oxygen utilization in terms of oxygen content during exercise was 31.8 per cent. The essential similarity between the two figures is further evidence for the normal response among this group of patients. The percentage utilization among these patients with sickle cell anemia is far below that which may occur among patients with little cardiac reserve who are exercised and who can meet conditions of stress only by increasing the peripheral utilization of oxygen.

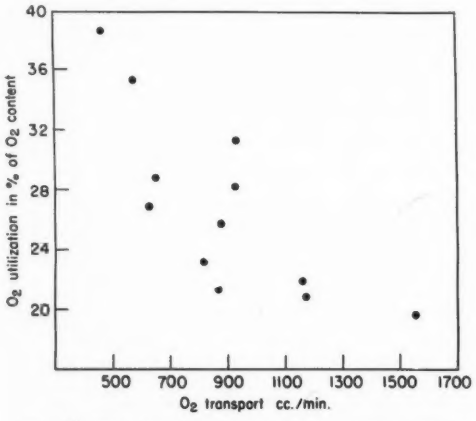

FIG. 3. Relation between oxygen transport to tissues and oxygen utilized, expressed as per cent of arterial oxygen content.

TABLE 4.—*Changes in Cardiac Output and Oxygen Consumption with Exercise*

Patient	Change in O_2 Consump. with Exercise cc./min.	Change in Cardiac Output with Exercise cc./min.	Change in Card. Output per 100 cc. Change in O_2 Consumption
D.H.	+95	+1100	+1158
B.A.	+166	+4900	+2952
J.P.	+247	+5400	+2186
E.F.	+101	+2800	+2800
P.B.	+160	+6000	+3750
C.H.	+140	+2700	+1929
S.T.	+123	−900	−732
I.E.	+196	+2000	+1020
B.G.	−28	−6800	
O.B.	+108	+500	+463
L.S.	+152	+3500	+2302
M.S.	+150	+5100	+3400

The work of the left ventricle in the majority of these patients was elevated at rest. This is in disagreement with the findings of Stewart and coworkers,[25] who studied a group of patients suffering from pernicious anemia. Since, in the range of 7 to 9 Gm. hemoglobin per 100 cc., the coronary blood flow is said to be normal or low and the oxygen consumption of the myocardium per unit weight low,[26] the efficiency of the heart among many of these patients must have been high. The fact that these patients were able to maintain an abnormally high level of cardiac work and efficiency for an indefinite period of time gives eloquent testimony concerning the reserve inherent in the human heart. At lower levels of hemoglobin, there is evidence that the coronary blood flow is high.[26] This is probably an important factor in maintaining cardiac reserve among anemic patients whose arterial oxygen content is so low that insufficient oxygen is available for extraction by the myocardium.

Whether the low resting arterial oxygen saturation observed in the majority of these patients is unique in sickle cell anemia is not clear. Other instances of the recording of low arterial oxygen saturation in sickle cell anemia have been found.[1, 29-31] The oxygen dissociation curve of sickle cell hemoglobin is reported to

be normal.[32] Although the oxygen saturation in anemia is said to be normal,[22, 27] Rasmussen[33] found the arterial oxygen saturation low in 6 of 12 resting patients with various types of anemia. Ryan[28] has presented evidence that the alveolar-arterial gradient in anemia is significantly increased and the oxygen tension of arterial blood decreased. Further studies to elucidate this point are contemplated.

The failure of the oxygen saturation to rise during exercise in some of these patients is in accordance with the findings of Himwich,[27] who found that the exercising oxygen saturation was lower than the resting saturation in five patients with anemia. This is probably due to increased venous admixture during exercise.[28]

Summary

1. Hemodynamic studies during the resting state have been carried out in 13 unselected patients with sickle cell anemia. Twelve patients were also studied during mild exercise.

2. The cardiac index at rest for the 12 patients considered to be in a basal state averaged 6.1 L. per minute per square meter of body surface area. The mean cardiac index during exercise rose to 8.1 L. per minute per square meter.

3. There was no demonstrable relationship between the resting cardiac output and the oxygen content or hemoglobin level. The percentage oxygen extraction by the peripheral tissues tended to vary inversely with the arterial oxygen content and the oxygen transported to the tissues per minute.

4. Nine of the 12 patients had a normal increase in cardiac output during exercise. One patient had an unexplained slight fall in cardiac output during exercise, and one a less than expected increase in output. One patient, who had a fall in cardiac output during exercise, was not in a basal state at rest. One patient, who increased his cardiac output during exercise, exhibited left heart failure during the exercise period.

5. Despite cardiomegaly and murmurs in all patients, cardiac catheterization failed to reveal any abnormality other than high cardiac output in all but two. One patient presented the hemodynamic pattern of cor pulmonale. Another of the series is presented as an example of concurrent organic mitral valvular disease and sickle cell anemia on the basis of hemodynamic and clinical data.

6. The mean resting arterial oxygen saturation was 91.7 per cent and was below normal in 9 of the 13 patients. The mean oxygen saturation during exercise was 91.6 per cent, 5 of the 12 patients experiencing a fall in saturation during exercise.

Sumario Español

1. Estudios hemodinámicos durante el descanso han sido llevados a cabo en 13 pacientes no seleccionados con anemia de hematíes falciformes. Doce pacientes también fueron estudiados durante el ejercicio moderado.

2. El índice cardíaco durante el descanso en los 12 pacientes considerados estar en condiciones basales fué 6.1 L. por minuto por metro cuadrado de superficie de cuerpo. El índice promedio durante el ejercicio aumento a 8.1 L. por minuto por metro cuadrado.

3. No hubo relacción demostrable entre la producción cardíaca durante el descanso y el contenido de oxígeno o nivel de hemoglobina. El porciento de extracción de oxígeno por los tejidos periféricos tendió a variar inversamente con el contenido arterial de oxígeno y el oxígeno transportado a los tejidos por minuto.

4. Nueve de los 12 pacientes tuvieron un incremento normal en producción cardíaca durante el ejercicio. Un paciente tuvo un ligero no explicado decremento en producción cardíaca durante el ejercicio, y uno un aumento menos de lo esperado en producción cardíaca. Un paciente, que tuvo decremento en producción cardíaca durante el ejercicio, no estuvo en condiciones basales durante el descanso. Un paciente, que aumento su producción cardíaca durante el ejercicio, mostró descompensación del corazón izquierdo durante el período de ejercicio.

5. No obstante engrandecimiento cardíaco y soplos en todos los pacientes, el cateterismo cardíaco no reveló ninguna anormalidad otra que una producción cardíaca alta en todos excepto dos casos. Un paciente presentó el

patrón hemodinámico de cor pulmonale. Otro de la serie se presenta como un ejemplo de enfermedad orgánica mitral valvular concurrente con anemia de hematíes falciformes a base de hemodinámica y datos clínicos.

6. El promedio de saturación arterial de oxígeno durante el descanso fué 91.7 por ciento y fué por debajo de lo normal en 9 de 13 pacientes. El promedio de saturación de oxígeno durante el ejercicio fué 91.6 por ciento, 5 de los 12 pacientes experimentaron una caída en saturación durante el ejercicio.

REFERENCES

[1] KLINEFELTER, H. F.: The heart in sickle cell anemia. Am. J. M. Sc. **203:** 34, 1942.

[2] OHRENSTEIN, I. R.: Incidence of sickle cell anemia with rheumatic heart disease. J. Pediat. **33:** 186, 1948.

[3] PLACHTA, A., AND SPEER, F. D.: The co-existence of rheumatic heart disease and sickle cell anemia. Am. J. Clin. Path. **22:** 970, 1952.

[4] YATER, W. M.: Sickle-cell anemia: A new cause of cor pulmonale. Am. J. M. Sc. **191:** 474, 1936.

[5] MARGOLIES, M. P.: Sickle cell anemia. A composite study and survey. Medicine **30:** 357, 1951.

[6] SHARPEY-SCHAEFER, E. P.: Cardiac output in severe anemia. Clin. Sc. **5:** 125, 1944–1945.

[7] BRANNON, E. S., MERRILL, A. S., WARREN, J. V., AND STEAD, E. A., JR.: The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. J. Clin. Investigation **24:** 332, 1945.

[8] HELLEMS, H. K., HAYNES, F. W., AND DEXTER, L.: Pulmonary "capillary" pressure in man. J. Applied Physiol. **2:** 24, 1949.

[9] FERRER, M. I., HARVEY, M. R., CATHCART, R. T., COURNAND, A., AND RICHARDS, D. W.: Hemodynamic studies in rheumatic heart disease. Circulation **6:** 688, 1952.

[10] SEELEY, R. D., NERLICH, W. E., AND GREGG, D. E.: A comparison of cardiac output determined by the Fick procedure and a direct method using the rotameter. Circulation **1:** 1261, 1950.

[11] VAN SLYKE, D. D., AND NEIL, J. M.: Determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. **61:** 523, 1924.

[12] DEXTER, L., WHITTENBERGER, J. L., HAYNES, F. W., GOODALE, W. T., GORLIN, R., AND SAWYER, C. G.: Effect of exercise on circulatory dynamics of normal individuals. J. Applied Physiol. **3:** 439, 1950–1951.

[13] REMINGTON, J. W., AND HAMILTON, W. F.: The evaluation of the work of the heart. Am. J. Physiol. **150:** 292, 1947.

[14] ITANO, H.: Human hemoglobin. Science **117:** 89, 1953.

[15] HUNTER, A.: The heart in anemia. Quart. J. Med. **14–15:** 107, 1945–1946.

[16] ELLIS, L. B., AND FAULKNER, J. M.: The heart in anemia. New England J. Med. **220:** 943, 1939.

[17] PORTER, W. B., AND JAMES, G. W.: The heart in anemia. Circulation **8:** 111, 1953.

[18] DEXTER, L., DOW, J. W., HAYNES, F. W., WHITTENBERGER, J. L., FERRIS, B. G., GOODALE, W. T., AND HELLEMS, H. K.: Studies of the pulmonary circulation in man at rest. Normal variations and the inter-relationships between increased pulmonary blood flow, elevated pulmonary arterial pressure, and high pulmonary "capillary" pressures. J. Clin. Investigation **29:** 602, 1950.

[19] COURNAND, A., RILEY, R. L., BREED, E. S., BALDWIN, E. DEF., AND RICHARDS, D. W.: Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. J. Clin. Investigation **24:** 106, 1945.

[20] HICKAM, J. B., AND CARGILL, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[21] LILJESTRAND, G., AND STENSTROM, N.: Clinical studies on the work of the heart during rest. III. The influence of variations in the hemoglobin content on the blood flow. Acta med. scandinav. **63:** 130, 1925.

[22] BLUMGART, H. L., AND ALTSCHULE, M. D.: Clinical significance of cardiac and respiratory adjustments in chronic anemia. Blood **3:** 329, 1948.

[23] LEWIS, C. S., JR., SAMUELS, A. J., DAINES, M. C., AND HECHT, H. H.: Chronic lung disease, polycythemia and congestive failure. Cardiorespiratory, vascular, and renal adjustments in cor pulmonale. Circulation **6:** 874, 1952.

[24] KROGH, A.: The supply of oxygen to tissues and the regulation of the capillary circulation. J. Physiol. **52:** 457, 1918–1919.

[25] STEWART, H. J., CRANE, H. F., AND DEITRICK, J. E.: Studies of the circulation in pernicious anemia. J. Clin. Investigation **16:** 431, 1937.

[26] BING, R. J.: The coronary circulation in health and disease as studied by coronary sinus catheterization. Bull. New York Acad. Med. **27:** 407, 1951.

[27] HIMWICH, H. E., AND LOEBEL, R. O.: The oxygen saturation of hemoglobin in the arterial blood of exercising patients. J. Clin. Investigation **5:** 113, 1927.

[28] RYAN, J. M., AND HICKAM, J. B.: The alveolar-arterial oxygen pressure gradient in anemia. J. Clin. Investigation **31:** 188, 1952.

[29] Fowler, N. O., Jr., Westcott, R. N., and Scott, R. C.: Pulmonary artery diastolic pressure: its relationship to pulmonary arteriolar resistance and pulmonary capillary pressure. J. Clin. Investigation **31:** 72, 1952.

[30] Reinhard, E. H., Moore, C. V., Dubach, R., and Wade, L. S.: Depressant effects of high concentrations of inspired oxygen on erythrocytogenesis. Observations on patients with sickle cell anemia with description of observed toxic manifestations of oxygen. J. Clin. Investigation **23:** 682, 1944.

[31] Tinsley, J. C., Jr., Moore, C. V., Dubach, R., Minnich, V., and Grinstein, M.: The role of oxygen in the regulation of erythropoieses. Depression of the rate of delivery of new red cells to the blood by high concentrations of inspired oxygen. J. Clin. Investigation **28:** 1544, 1949.

[32] Itano, H.: Personal Communication.

[33] Rasmussen, H., and Sturstein, O.: Studies in oxygen therapy. Part II. On the effect of oxygen therapy on the oxygen unsaturation of the arterial blood. Acta med. scandinav. **141:** 52, 1951.

The Sixty-Ninth Mary Scott Newbold Lecture

The Mechanism of Cardiac Failure

By Louis N. Katz, M.D.

IT is a privilege to have been asked to give the sixty-ninth Mary Scott Newbold Lecture. The list of my predecessors is indeed distinguished. The topic, cardiac failure, was chosen because my colleagues and I have been concerned with this problem for almost a quarter of a century. In this lecture I propose to outline my present concepts based on the evolution of thinking which has resulted from our work in this field and the impact of the literature. I shall give scant attention to the work of others, not because their work is unimportant, but because time is limited and the material to be covered extensive.

What Is Cardiac Failure?

At the outset, let us define the task of the heart. It is the task of the heart to supply an adequate quantity of blood to meet the requirements of the various organs in the body at rest and during activity, so that they may perform their several functions without handicap. A heart that does this is *competent*. One that does *not* is *incompetent*. Incompetence of the heart includes another concept. An incompetent heart is not only one that fails to pump an adequate amount of blood to the organs because the compensatory mechanisms are inadequate, but it may be one which does its assigned task, provided the compensatory mechanisms are adequate. Encroachment upon cardiac reserves occurs, therefore, whenever the heart becomes incompetent.

An incompetent heart with an inadequate output exhibits "forward failure" phenomena. An incompetent heart with an adequate output exhibits congestive phenomena behind the incompetent chamber. An incompetent heart with an inadequate output may show such congestive phenomena also, in addition to "forward failure."

Failure of the circulation in supplying the organ needs at rest or during effort may be cardiac or extracardiac. *Extracardiac circulatory failure* may be due to peripheral vascular collapse, when the systemic peripheral vessels dilate and blood is pooled within them instead of being returned to the heart. It also occurs in shock, which should be clearly defined as a progressive oligemia with hemoconcentration and compensatory systemic vasoconstriction. Here too the decreased venous return to the heart is the primary mechanism for the inadequate circulation. In both of these circumstances, the inadequate circulation is not initially due to an incompetent heart, but is due to circulatory disorders in the vascular system. Thrombosis in major veins, or other forms of venous obstruction, is another mechanism interfering with the venous return to the heart, and may lead to circulatory failure without the presence of an incompetent heart.

Cardiac circulatory failure, in which the inadequate blood flow is due to an *incompetent heart*, need not always be myocardial in origin. It may also be due to: (1) a dynamically significant valvular dysfunction, as in severe stenosis or free regurgitation; (2) a pericardial tamponade, a concretia cordis or a constrictive pericarditis; or (3) a tachycardia with its associated reduction in minute-filling time.

The recent trend of semantics in which the terms congestive failure, low output failure and high output failure, have come into vogue, has led to some confusion to the uninitiated, and these terms should be dropped. Low output failure is a loosely used concept, including many things. Low output of the heart may ensue for a number of reasons and need not be pri-

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marily cardiac. When, however, in the course of shock or peripheral vascular collapse, or any other extracardiac mechanism leading to low output, incompetence of the heart ensues, then the latter can contribute to the low output.

High output failure is a misnomer that can only confuse the issue. High output of the heart is a compensatory mechanism which enables the body to get an adequate supply of oxygen for the tissues, when this is impossible at normal levels of output. This may ensue in arterial hypoxemia (e.g. anemia, inadequate ventilation in the lungs), in hyperthyroidism and in some avitaminoses. In some fashion the output of the heart per minute is augmented in these circumstances. If the strain is too much for the heart then it becomes incompetent and cardiac circulatory failure ensues even though the cardiac output may still be above the average normal. Chronic cor pulmonale is a frequent example of this circumstance.

Congestive failure too is a misnomer. Congestion may accompany incompetency of the heart whether or not there is cardiac circulatory failure. It may also ensue from disorders of the vascular system when the heart is competent. The mechanisms are in part vascular and in part renal; the latter are dealt with below. The former represent damming up behind the obstruction, whether this be a narrowed vein, a stenosed valve or an incompetent chamber of the heart, with the resulting consequences of this congestion. It may be behind the left or behind the right heart. Such congestion in the pulmonary veins impairs the ventilatory indices, increases the residual volume of the lungs, decreases the vital capacity and leads to pulmonary edema, first manifested by rales. It also leads to elevated "wedge" pressure and often to pulmonary arterial hypertension. Such congestion in the systemic veins leads to venous hypertension and engorgement, liver enlargement, anasarca and edema, as well as to interferences with the most effective operation of the various organs including the heart itself. Such states have been called respectively "left" and "right heart failure."

Not only is the heart attuned to put out as much blood as it receives when in dynamic equilibrium, but this applies equally to each individual side of the heart. Thus, in dynamic equilibrium, the right and left ventricles pump out equal amounts of blood, whether this is low, high or average. Only when a patient is going into circulatory failure, coming out of it, or is moribund, is there any extended period of disequilibrium between the two hearts, as far as their minute output is concerned. So called "right" or "left heart failure," or more properly circulatory failure due to right or left heart incompetency, therefore, is not a disparity in output of the two sides of the heart. A moment's reflection will show that if the left heart were to pump 5 cc. more per stroke than the right, and if the right ventricle pumped 60 cc. per stroke and the heart beat 80 times per minute, and if the circulating blood volume is of the order of 5 liters, then in about 10 minutes all of the blood would have been pumped into the systemic circuit and none would remain in the lungs. This *reductio ad absurdum* is simply mentioned because of the loose thinking sometimes encountered in dealing with this subject.

One of the problems that has become of practical significance latterly, is the identification of how much of the lung congestion is due to mitral stenosis or mitral regurgitation and how much is due to a myocardial incompetent left ventricle. Furthermore, as every clinician appreciates, pulmonary disease itself produces signs, symptoms and changes in the laboratory measures of ventilatory efficacy in many respects imitative of that produced by an incompetent left heart.

It is thus apparent that heart failure arises from incompetency of the heart, sometimes leading to cardiac circulatory failure—an entity distinct from extracardiac circulatory failure—and sometimes leading to congestion. Furthermore, it should now be clear that not all forms of incompetency of the heart are due to *myocardial* incompetency; they may result from abnormalities of other parts of the heart's structure or from disturbance in its rhythm. Finally, even the normal myocardium may be put to so much strain that its reserves are exhausted, and it too can become incompetent

under these excessive conditions of stress. The distinction between a normal and a diseased myocardium is that the stress required to lead to this breaking point is less for the diseased than for the normal myocardium.

Regulation of the Normal Cardiac Output

The heart normally is so attuned that it pumps out, over any extended period of time, as much blood as it receives. In this respect, it is no different than the peripheral circulatory tree, which ordinarily forwards to the heart as much blood as it receives over any extended period of time. A number of servomechanisms are involved in this fine attunement of the circulation. Some of these are mechanical, some are humoral and some are neurogenic.

The most important of the humoral mechanisms are those involving the hormones of the adrenal medulla, *l*-epinephrine and *l*-norepinephrine, although doubtlessly other hormones, especially those of the adrenal cortex and pituitary, play their role. Closely bound up with the adrenal medullary hormones are the autonomic nerves which richly innervate the heart and peripheral blood vessels. They are linked with end organs, both chemo- and baroreceptors, located in the lungs, in the pulmonary and systemic vascular trees, and in the heart itself. The autonomic nerves are also influenced by messages relayed from end organs located in various somatic structures, and including the special senses. They are also subject to the outpourings of the several stations in the central nervous system which constitute a complex cybernetic arrangement, far more complicated than that used by engineers.

A little more needs to be said about the mechanical factors controlling the flow of blood in the periphery. The capacity of the peripheral vascular bed is subject to change by humoral and neurogenic influences. This can occur by opening or closing of blood reservoirs and so adding to or extracting blood from that in active circulation. In like manner, changes in venomotor tone may strikingly alter the capacity of the peripheral vascular bed, shifting blood to or away from these vessels, which constitute a large variable capacity. Similarly, vasomotion in the smallest vessels may be enhanced, leading to accelerated forward flow. This acceleration of forward flow is brought about by virtue of the presence of valves in the circulatory tree which convert any intermittent forces operating upon the blood into forward flow. Such intermittent forces may also be caused by the movements of the innumerable villi in the intestines, by the partial tetanic contraction of the skeletal muscles which gives them their tone, by the motions of the limbs as in walking, and by the swaying accompanying the maintenance of an upright stance. Just as significant is respiration itself, since the thorax and abdomen can be considered as alternating bellows. Even the heart plays its role in this regard, over and above the *vis a tergo* it imparts, some of which still remains when the capillaries are reached. Thus, during its systole, the auriculoventricular junction moves toward the apex, tending to cause a drop on the pressures within the atria and thereby facilitating the flow of venous blood toward the heart.*

There are thus a number of factors which adjust venous return to the heart and act as a powerful adjuvant to the pumping power of the systole of the ventricles. To them must be attributed a major part in maintenance and regulation of blood flow.

Adjustment of the heart itself also plays an important role in regulating the cardiac output. In part, this is brought about by variations in *heart rate*, which is dependent upon the action of the nerves supplying the heart, aided and abetted by the adrenal medullary hormones. In part, cardiac output is dependent upon the size of the ventricles when systole begins, that is, upon the right and left ventricular *end diastolic volumes*. This in turn is dependent upon the *systolic residue* (the blood not pumped out in the previous systole), the *tone* of the ventricles which determines its resistance to

* This motion of the base of the heart toward the apex during systole has another pumping effect: the aorta and pulmonary artery are elongated while their valves are open, so that when these vessels shorten again in diastole with the valves closed, a small amount of blood is, as it were, "lifted" and added to that already ejected by the heart during its systole.

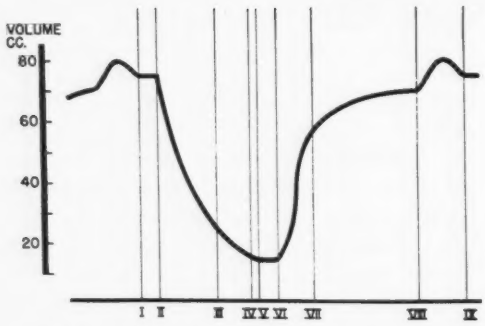

FIG. 1. Diagram of the volume curve of one ventricular cavity of the human heart at an assumed rate of 80 beats per minute, a stroke volume of 60 cc. and a systolic residue of 15 cc. (Based on the studies of Wiggers and Katz.[2]) The curve starts in diastole. When the impulse in the sinus node spreads to the atria it causes them to contract and then relax (between VIII and IX and the homologous part of the curve ahead of I). The atria contribute little to filling; about 5 cc. net at ordinary heart rates. Actually while they add 10 cc. during their contraction, they "take back" 5 cc. during their active relaxation. The impulse reaches the ventricles at I, and they begin to contract, at first isometrically (between I and II). Then ejection begins. In the short period of time, from II to IV, the blood is ejected from the ventricle (except for the systolic residue). Most of the blood is expelled during the rapid ejection period (II to III) and the remainder in the reduced ejection period (III to IV). Diastole begins at IV with a short protodiastole phase (IV to V) and an isometric relaxation period (V to VI). Most of the filling of the heart occurs in the rapid inflow phase (VI to VII). Filling here is just as brusque, and the period of filling is just as short, as that of the rapid ejection phase. In other words, the heart fills with a rush over a short period and not deliberately and uniformly over the whole of diastole. After rapid inflow, there is the period of passive filling, diastasis (VII to VIII), due to the vis-a-tergo of the blood coming back to the heart.

filling, and the *duration of diastole*, especially the period of its rapid inflow phase (fig. 1). In addition to the action of end diastolic volume and heart rate, both of which are partly determined by extrinsic conditions lying outside the heart, there is another mechanism altering cardiac output which is dependent upon change in the *contractile power of the heart*. This last is affected by extrinsic influences, resulting chiefly from alterations in the tone of the cardiac nerves and in the hormonal content, especially of adrenal medullary hormones, present in the blood irrigating the heart.

In order for the heart to adjust its cardiac output, alterations in its energy releases take place. These, as ordinarily measured in terms of cardiac oxygen consumption, are determined not only by the end diastolic volume of the ventricles, but also by the character of the actual contraction of the ventricles and by extracardiac neurogenic and humoral mechanisms. When the work of the heart is measured in terms of the product of cardiac output and blood pressure in the aorta and pulmonary artery, and this is compared with the oxygen consumed by the heart to do this work, it is found that the ratio of work to oxygen consumed is quite variable at any end diastolic volume. In fact, oxygen consumption may go down as work increases even though heart size is augmented and heart rate unchanged. This demonstrates that cardiac oxygen consumption like cardiac output is determined by other factors in addition to end diastolic volume.

WHAT DISEASE OF THE HEART DOES

Let us now turn to disease of the heart and see what it does. Disease may increase the stress upon the heart. It may lead, for example, to systemic hypertension. It may lead to pulmonary arterial hypertension which catheterization has demonstrated to occur often; pulmonary arterial hypertension is a frequent complication of a strained left heart, and has as its clinical measure, crude though it be, accentuation of the second pulmonic sound. Disease may lead to increased venous return because often the body metabolism is increased; metabolism is increased either because of the dyspnea produced, the restlessness of the patient, or an associated hyperthyroidism. Added to this, there is an increased venous return whenever anemia or hypoxemia complicates the picture, or when there is a chronic cor pulmonale. Certain vitamin deficiencies are another cause for increases in venous return in heart disease. In addition, disease may lead to valvular stenoses, valvular regurgitations, obstructions, atresias, coarctations, and shunts.

These hidden stresses must be uncovered from their concealment by the examining physician.

The diseased heart will respond to these loads in the same way as the normal heart. It will call for a mobilization of compensatory mechanisms much as in the case of the normal heart. By so doing it will cut down the cardiac reserves.

Disease of the heart may decrease the upper limits of the adjusting compensatory mechanisms from which benefits may be derived and in this way also reduce the cardiac reserve. Thus, for example, the turning point from benefit to detriment as far as heart rate is concerned will occur earlier. This is demonstrated constantly by the relatively greater seriousness of paroxysmal tachycardia of equal degree in hearts that are diseased, than in those that are not. In the case of hypertrophy, the presence of serious coronary disease leading to narrowing of the arteries will summate with the normal factor limiting hypertrophy, so that there will be less chance for maximal hypertrophy than in the normal heart. (Heart weight is a deceptive measure of heart hypertrophy since it also weighs tissues in the heart other than muscle, viz., fibrosis and necrosis. Proper evaluation of true hypertrophy should take this into account.) The upper limit of dilatation is also reached sooner in some forms of heart disease. It would seem that under certain circumstances the heart cannot dilate as much when it is diseased as normally, before reaching the point where the dilatation is detrimental rather than beneficial. While too little is known about the detailed effect of disease upon the heart's contractile power, it is obvious that if the machinery of the heart is impaired, the effectiveness of extraneous mechanisms in increasing contractile power may be lowered. Thus, in several ways, disease of the heart by reducing the maxima of compensation from which benefits may be derived, cuts down the reserve of the heart.

Finally, disease of the heart may impair the contractile power of the heart. When it leads to an obvious anatomic defect like myocardial infarction, which may destroy the machinery of up to one-fourth or more of the left ventricle, the defect in contractility is obvious and apparent. Disease may operate more subtly without such gross change. This may be revealed as cloudy swelling or fatty degeneration histologically, but often it is more subtle than this in lessening cardiac contraction and relaxation. We know so little about the details of the chemistry of this machine, that I will not indulge in any speculations on this topic. When heart disease alters the contractile machinery of the heart, the heart may work inadequately. The heart compensates for an impairment in contractility in the same manner as it does for an increase in stress. At the bedside, therefore, the demonstration of compensatory mechanisms may indicate an increase in stress upon the heart or an impairment in its contractile power.

Stress on the Heart and the Manner of Meeting It

In order to understand better the subject of myocardial incompetence and the sequences resulting therefrom, I think we must turn to the normal heart and consider the stresses to which it is subjected and the compensatory mechanisms by which it meets these stresses. Stress upon the heart is threefold in character. It may be due: to an increase in venous return, i.e., in its input load; to an increase in the blood pressure of the systemic or pulmonary arterial system, i.e. in its resistance load; or to certain hidden loads not so easily revealed. Exercise and many emotional disturbances produce an increased input load. They also lead to an increased resistance load on the left heart and often also on the right. Trauma may produce some hidden loads in an otherwise normal heart.

These increases in load have been reproduced in the experimental animal and the mechanisms by which they are met studied. What are these compensatory mechanisms? They are four in number:

1. There is dilatation.
2. If time elapses, there is hypertrophy.
3. There is tachycardia.
4. There is an increase in the contractile power of the myocardium produced by hormonal, humoral or reflexogenic mechanisms.

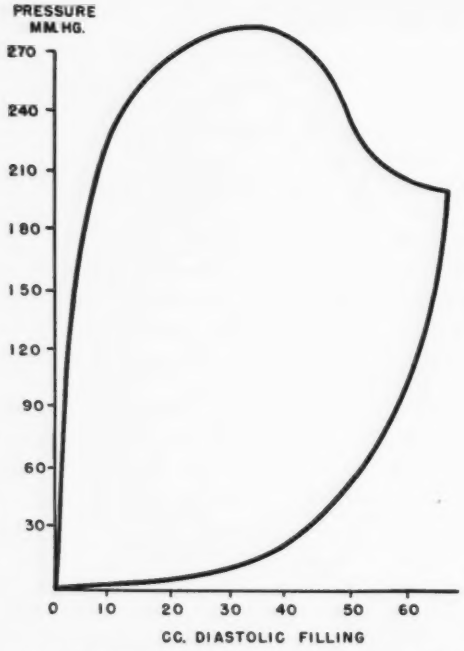

FIG. 2. A diagrammatic representation of the distensibility (P/V) curve of the fully relaxed (lower) and fully contracted (upper) left ventricle. It will be seen that at volumes between 0 and 20 cc. the change in pressure at the end of diastole is minimal. Only above 40 cc. does the pressure change become marked. On the other hand, the pressure change at the end of systole is marked at volumes between 0 and 10 cc., reaching a maximum at about 35 cc. and then declining. In isobaric contraction the change in volume during systole and diastole is set on a horizontal line at the level of pressure at which the heart contracts and relaxes, the limits being determined by the two P/V curves. In isovolumetric contraction the change in pressure during systole and diastole is set on a vertical line at the level of the diastolic filling at which the heart contracts and relaxes, the limit being determined by the two P/V curves. Under ordinary conditions of the heart beat, a closed figure is set up (a work-diagram) which begins and ends at the fully relaxed P/V curve, and is determined by the conditions under which the heart begins its systole. The shapes of the systolic and diastolic portions of the curve, and the point where the curve of the work-diagram intercepts the fully contracted P/V curve, are determined by the conditions under which its contraction and relaxation take place. (Copied from Patterson and Starling, J. Physiol. **48**: 465–513, 1914.)

These same mechanisms, as already hinted, operate also upon the diseased heart when its load is increased or when its contractile power is impaired. Dilatation is a simple mechanism resident in the heart and can be seen in the isolated heart, and so may be considered a primary mechanism which is able to attune the output of the heart to its input. At the bedside, dilatation of the heart should be considered compensatory to enable the heart to meet an increased load. In this modern era of catheterization, too many physicians imagine that the pressures in the heart at the end of diastole are a good measure of the size of the heart at that time. Actually the relationship between the end diastolic volume and the end diastolic pressure is not linear, but curvilinear (fig. 2). There is, therefore, under ordinary circumstances, little or no change in the end diastolic pressure with rather large changes in end diastolic volume. It is to the end diastolic volume change that the ventricle's energy release, ability to work and pump blood, is related, and not to its end diastolic pressure. The difficulties of obtaining information regarding end diastolic volume should not permit loose employment of end diastolic pressure, or worse still, the average or mean atrial pressure as an index of the adjustment of the heart by dilatation to an increased load, an error that has unfortunately crept into modern thinking on the part of certain individuals.

Hypertrophy is another mechanism which, by increasing the mass of the heart, permits it to release more energy so that it can overcome the increased load. It requires time, however, and is not available at once but comes into play progressively if the load is sustained over time. We do not know the mechanism of cardiac hypertrophy, although we have reason to believe that it is associated with dilatation, with relative hypoxia and with relative increase in the work of the heart, and is, in some fashion, induced by the release of certain hormones of the pituitary gland. The mechanism of hypertrophy needs intensive exploration. Hypertrophy will occur in a normal heart subjected to increased load as well as in a diseased heart. Obviously, therefore, both

dilatation and hypertrophy are not necessarily signs of heart disease unless it is clear that they occur without an increased load upon the heart.

Tachycardia which operates in the intact animal, and is not seen ordinarily in the isolated denervated heart, is a mechanism brought about in some fashion by an increased load. It would take us too far afield in this discussion to enter into the several mechanisms by which this tachycardia could be produced. Suffice it to say that it involves a lessening in tone of the cholinergic nervous mechanism and an enhancement in tone of the adrenergic nervous mechanisms, in all likelihood aided and abetted by the release of *l*-norepinephrine and *l*-epinephrine, with the possibility of other humoral agents also operating. Tachycardia, too, is to be considered a compensatory mechanism as easily available as is dilatation to permit the heart to overcome an increased load.

Closely allied with this are changes in the intrinsic machinery of the heart, part of which may operate upon the viscous-elastic properties which we call its tone, but more primarily they operate upon the machinery of its systole, its contractile power. Like tachycardia, these changes in the contractile power of the heart are brought about by reflexogenic and hormonal mechanisms, and it would have been surprising indeed if in the intact animal this had not developed. It is not too difficult to show, upon the exhibition of sympathetic nerve stimulation or the administration of ordinary epinephrine, as I did as far back as 1918, that such changes can be produced in the contractile power of the heart without dilatation and independent of the tachycardia (fig. 3). Exactly how this is brought about and upon which part of the intricate machinery of fat and carbohydrate metabolism—whether upon glycolysis, the Krebs cycle, the actinmyosin mechanism, or the ionic milieu surrounding the muscle—remains to be clearly established. Our department is now engaged in a long-term evaluation of this problem. Suffice it to state that tachycardia and changes in contractile powers of the heart, which are extracardiac in their mechanism, play as important a role as do the intrinsic adjustments of dilatation and hypertrophy.

When all four compensatory factors are simultaneously operative, they are interdependent; the more there is of one, the less need there is for the others to come into play. It would appear that dilatation is one that gives way, the one that is held more in reserve; so is tachycardia. Thus, for example, we are all aware of the fact that a patient with essential hypertension may for years have no tachycardia or no dilatation of his heart, the compensatory mechanism to meet the increased resistance load being accomplished by hypertrophy of the left ventricle.

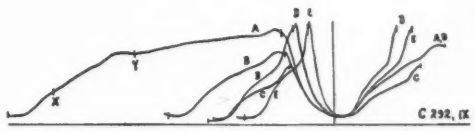

FIG. 3. A series of volume curves of the open-chested anesthetized dog drawn so as to superimpose the end of systole of the several beats, in order to show the effect of vagus stimulation (A and B) and epinephrine effect (D and E), as compared with the control (C). Attention is drawn primarily to the shorter duration and accelerated rate of ejection which was produced by epinephrine. These changes are disproportionate to the changes in heart rate and end diastolic volume, indicating a specific action of epinephrine upon the contractility of the heart (from Wiggers and Katz[2]).

CARDIAC RESERVE

One of the concepts that has been loosely employed is the term cardiac reserve. From our work and the impact of this work upon our thinking, I believe, cardiac reserve can be defined more precisely in terms of dilatation, hypertrophy, heart rate and contractile power, since for each of these there is an upper limit beyond which further increase is not possible or, if possible, it becomes detrimental instead of beneficial. Cardiac reserve according to this concept is the difference between the size of the heart existing under the given load and the upper limit from which benefit can be derived; it is the difference between the heart weight existing under the load and that which can be produced; it is the difference between

the heart rate existing under the load and the upper limit of heart rate from which benefits can be derived; and it is the difference between the contractile power of the heart existing under the load and the maximum that can be obtained. More properly, however, it is the sum of these four measures of cardiac reserve that gives an index of the total cardiac reserve available to meet increased loads. Now, admittedly it is not always possible in our present state of knowledge to define clearly these measures of cardiac reserve, but this in no sense nullifies the merit of such a concept.

A few words are not amiss concerning the reasons why there is an upper limit to each of these compensatory mechanisms. Thus, it has been established that the heart cannot dilate indefinitely and produce an increase in work. Actually, after a certain point, further dilatation leads to a decline in work (fig. 2). An optimum thus exists in the size of a heart below which further dilatation is beneficial, above which it is detrimental. This fact has been established beyond question. It has been found to be true also when skeletal muscle is lengthened. I like to think in terms, therefore, of a dilated, compensated heart, and an overdilated, failing heart.

The upper limit of hypertrophy is due to the fact that the number of capillaries do not increase as the heart hypertrophies. This inability of the capillaries to increase in number as the heart mass increases, puts an upper limit to the continued increase in heart weight. This is so since the oxygen and nutritive materials in the blood, and the carbon dioxide and waste products in the tissues move from one site to another by simple diffusion, dependent on their relative concentration at the two sites. As a consequence, the tissues further removed from the capillaries are less well serviced than those close to the capillaries, and as the distance from the capillaries increases, a point will be reached in which the material is not supplied or the waste not removed in adequate amounts commensurate with proper functioning. It is on this basis that the maximum mass of the heart is limited.

When it comes to the extracardiac mechanisms leading to increase in cardiac contractile power, the limits have not been thoroughly explored, but it is just a matter of logic to conceive that these stimuli cannot continue indefinitely to increase the power of the heart. An upper limit must of necessity be reached. What it is, and how much greater than the ordinary contractile power of the heart it will be, remain to be clearly defined.

In the case of heart rate, a number of considerations come into play to point out that one cannot continuously increase the heart rate and get benefit therefrom. This depends in part upon the shape of the filling curve of the ventricles (fig. 1) from which, if we ignore compensatory mechanisms as a first approach to our understanding, it will be seen that as the heart speeds up, it affects at first only an abbreviation of diastasis. Consequently the minute output will go up. This is so since stroke output depends on diastolic filling. When, however, the rate becomes so rapid that it cuts more and more into the rapid inflow phase, then the product of stroke volume and heart rate will decline. In fact, if the rate is so rapid that diastole consists only of isometric relaxation, then no filling will ensue and the heart will therefore have to draw upon its systolic residue for emptying, and this can soon be exhausted within a few beats. Thus, in this department, we have recorded pressure curves from the aorta in man during premature systoles which occurred so early that no evidence of a pressure rise was seen. Compensatory mechanisms tend to overcome this mechanical obstacle of tachycardia, but even they cannot ultimately prevent this decrease in minute volume output with acceleration of the heart. That this is so is shown by the fact, as all of you know, that paroxysmal tachycardia can lead to circulatory failure, and/or to congestion—which can be remedied immediately upon the conversion of the tachycardia to the slower sinus rate.

Tachycardia also becomes detrimental because it cuts down the recovery time. The heart has very little ability to go into oxygen debt. It must make up in the next diastole or two for the oxygen for which it goes into debt during its systole; and since it is constantly beating, this cannot be out of balance for

long without setting up a progressive deteriorating mechanism. Now, as the heart accelerates, the acceleration is primarily at the expense of diastole when recovery occurs, since systole varies only with the square root of the cycle length. Thus, progressive tachycardia puts an increasing strain upon the recovery mechanisms of the heart, and a rate will ultimately be reached that will make the strain so great that the heart cannot by this mechanism meet the increased load.

Furthermore, with tachycardia it is clearly established that the mechanical efficiency, estimated in terms of oxygen consumed for work done, declines progressively as the heart accelerates. Further, it is established without controversy that as the heart progressively speeds up, insufficiency of its coronary blood flow eventually ensues. Hence, not only is there strain upon the recovery time with acceleration because of less time to recover, but there is greater need for oxygen to do the work and there is less adequate coronary flow to permit this recovery to take place.

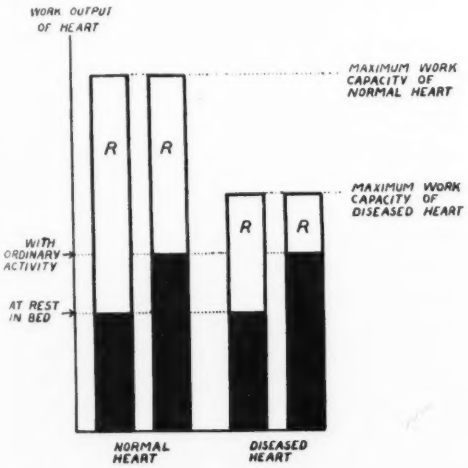

FIG. 4. Factors determining cardiac reserve (R) in the normal and diseased heart (from Katz[18]). The reduction in R between bed rest and ordinary activity is shown both for the normal and for the diseased heart. Note, however, that the maximum capacity is reduced by disease. Cardiac reserve applies to all the compensatory mechanisms whether it be dilatation, hypertrophy, tachycardia, or change in contractile power. Discussed in text.

CONSEQUENCE OF INADEQUATE COMPENSATING MECHANISMS

Thus, it will be seen that the adjustments of the heart which compensate for an increasing load are limited in extent and when these limits are exceeded and when the reserves of the heart are exhausted, the heart cannot meet any further increase in load (fig. 4). The classification of the American Heart Association could be viewed in these terms. With increasing load the upper limits for compensation are reached earlier in the class IV patient than in the class III or class II patient (fig. 5).

With progressive encroachment upon the cardiac reserve, a point will be reached when the compensatory mechanisms become inadequate. With inadequacy of the compen-

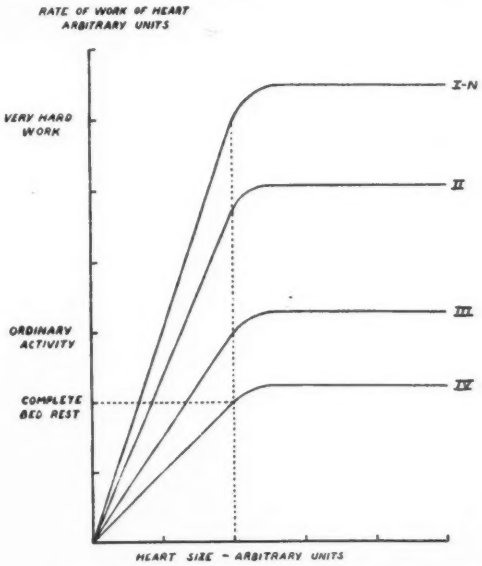

FIG. 5. Relation of work done to heart size in normal subjects (N) and patients with heart disease falling into classes, I, II, III, and IV of the American Heart Association Classification (Katz[15]). In class I, the individual has the normal limitation in his ability to carry on activities. In the other classes—II with slight, III with moderate restriction of activity and IV requiring complete bed rest—the work done by the heart progressively declines at a given heart size. Therefore, to do the same amount of work as the patient in the class with less impairment of the heart, the patient requires a larger heart size. This encroaches on cardiac reserve. Discussed in text.

sating mechanisms, whether brought on by an increase in load, a decline in the maxima of compensatory mechanisms, or a decline in contractile power of the heart, a new chain of events will ensue. There will develop cardiac circulatory failure, at first only during periods of stress, but later also during ordinary activity and ultimately even at bed rest. Death will then not be far away.

Even before this, redistribution of the circulating blood volume will take place. Blood will be brought out of the reservoirs and the venules by neurogenic and humoral mechanisms in an attempt to bring about compensatory dilatation of the incompetent chamber of the heart. This blood together with the blood damming up behind the incompetent side of the heart leads to congestion and its sequelae (see above) and in some fashion also disturbs the excretory function of the kidney (see below). Thus, when the heart becomes incompetent, there is set up a complex chain of events involving many parts of the circulation and requiring the interplay of many humoral and neurogenic regulating mechanisms. Much remains to be learned concerning this phase of cardiac failure.

The Mechanical Efficiency of the Incompetent Heart

I would like to turn now to the subject of the changes in the mechanical efficiency of the incompetent heart, a subject that has been rather forcefully debated in recent years. There are those who believe that heart incompetency is primarily the result of an impairment in the ability to employ for useful work the energy released. There are others, like myself, who believe that the primary defect is in the release of energy and that the ability to employ this energy for work is not *primarily* impaired in *all* instances of heart incompetency. This is a fundamental problem which may have to be reinterpreted as our knowledge of the intermediate metabolism of the heart grows and clarifies. I will not belabor you with many of the fascinating details of this controversy, but I would like to leave you with a few facts for orientation.

Mechanical efficiency, as an engineering term, is defined as the ratio of work done to the energy required to do this work, the quotient being calculated in similar units, e.g., Joules, foot-pounds or large calories. The energy cost is ordinarily measured in terms of oxygen consumed, and it is assumed that the respiratory quotient is constant in the incompetent as compared with the competent heart, and this quotient may be assumed to be 1 or, as in the case of the average heart, 0.82. The term *work* has had many definitions, but it is more or less generally agreed that it should be defined as the useful work of the heart; that is, the amount of blood pumped by the heart multiplied by the mean blood pressure. The omission of kinetic energy in this calculation ordinarily introduces no serious quantitative error. In our calculations we have included the work of the right as well as the left heart, and have included the coronary flow in calculating the latter. Obviously by using this method of mean values in calculating the work, instead of integration formulas, certain other errors creep in, but these are not ordinarily of sufficient moment to disturb the concept.

Using the simple method outlined above to calculate mechanical efficiency, it can be shown that mechanical efficiency can decline if tachycardia accompanies heart failure, as is often the case (fig. 6). But this is not primarily due to the heart failure, since tachycardia in a competent heart will have a like effect. Likewise it can be shown that if the cardiac output per minute declines as the heart fails, the mechanical efficiency will decline (fig. 6), but this too is not primary with failure, since it will occur with low output even in the competent heart, as in cases of early shock. Furthermore, if an increase in the pulmonary or systemic arterial pressure, an increase in resistance load, occurs, this too may have a tendency to alter the mechanical efficiency in a downward direction (fig. 6), but this again is not primarily heart failure, since a similar effect will occur under like circumstances in the competent heart. In our own experience, with isolated hearts whose work has been kept constant despite their progressive incompetence, we have found no

change in the oxygen consumption of the heart even though the heart dilated in order to maintain this work.

How can we be sure that incompetence is of the same character in all circumstances? Actually, I believe it is not. It may develop in one fashion under certain conditions and in another fashion in other circumstances. It is erroneous to assume that incompetence of the heart is identical under all conditions.

When we view the mechanical efficiency of the heart even under the best circumstances, we find that it really is at most of the order of 30 per cent. Apparently the rest of the oxygen, or a large part of it, is used to maintain the machinery in repair, i.e., to make up for the wear and tear of the machinery, and not directly for its work. Hence, as the work of the heart declines, there may be a *pari passu* decline of the oxygen needed for the work, but the reparative processes may go on at the same level as before and so the total oxygen may not go down as much as the work does; hence the efficiency will decline. The contrary will be the case when the work of the heart is increased. Here the proportion of energy needed for work will be increased and that necessary for the reparative processes will be less, percentagewise. Furthermore, to pursue these theoretic concepts, there is no guarantee that the rate and sequence of the many intermediate chemical reactions involved during the systole and diastole of the heart will be the same in the incompetent as in the competent heart, or that even the same reactions are employed; and these circumstances obviously can lead to changes in the mechanical efficiency which may vary from one type of incompetent heart to the next, depending upon how the machinery is deranged. Therefore, the mechanical efficiency of the incompetent heart changes in a very complex fashion, especially when cardiac circulatory failure supervenes, all the details of which are not yet clearly understood.

It therefore behooves the clinician in his every day activities to avoid the term *cardiac efficiency* and speak more of the *efficacy* of the heart, a term which need not be confused with the more precise definition to which engineers have assigned the concept of mechanical efficiency. I would predict that in the coming years we will have considerable clarification of this aspect of the mechanics of the incompetent heart as newer knowledge of the intermediate metabolism of the heart advances.

Edema Formation

In the final portion of this lecture I would like to turn to a different aspect of heart failure, edema formation, in order to emphasize that the syndrome of heart failure is a derangement of function occurring in a complex and interlocking fashion, and extending beyond the heart and the vascular tree. While the heart is the initiating mechanism, a chain of alterations is set up which makes the syndrome of heart failure much more than primary incompetence of the heart. This is not to say

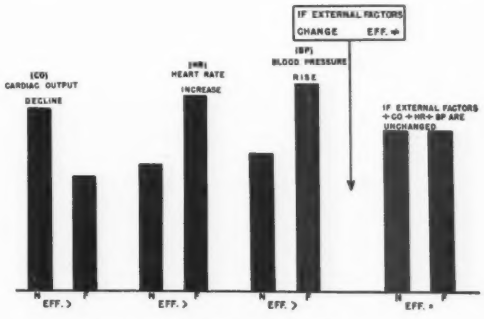

FIG. 6. The three sets of columns compare respectively, the cardiac output (CO), the heart rate (HR) and the systemic arterial blood pressure (BP) in cardiac circulatory failure (F) and normal circulation (N). The change in each is such as to decrease (>) mechanical efficiency (EFF) of the heart during failure. But like changes in these factors in the competent heart will have a similar effect on efficiency. A number of external factors which can change when the heart fails and thereby alter mechanical efficiency are represented in the square. Since their influence is not known, mechanical efficiency is marked as being changed (≠). There is no reason to believe that similar effects would not be produced by such factors in the competent heart. In the last pair of columns is shown a situation actually obtained in the isolated heart (from Katz[13]) in which the variables—external factors, cardiac output, heart rate and blood pressure —were kept constant and the mechanical efficiency, consequently, remained unchanged (=). Discussed in text.

that one must concentrate on the secondary mechanisms and forget the primacy of the heart, but it shows that heart failure like other syndromes is complicated and not simple. This can best be illustrated, I think, by discussing the mechanisms of cardiac edema. This is a subject with which this department has been concerned for a considerable period of time.

The heart initiates the mechanism which causes retention of water and sodium chloride, but this retention is in reality due to a disturbance in the kidney regulation, whose task it is to see that water and sodium chloride neither accumulate nor are depleted from the body. How does this come about? Recently it has been attributed to cardiac circulatory failure ("forward failure"), at least that occurring during periods of stress. It has been emphasized that under these circumstances

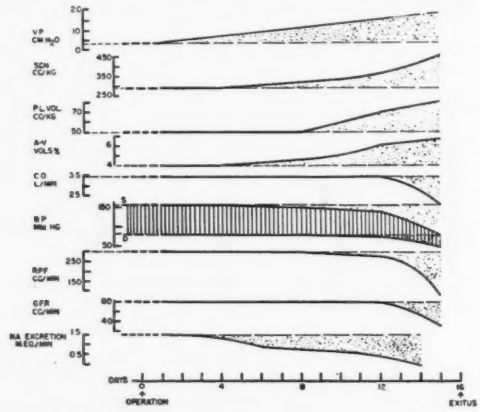

FIG. 7. Sequence of physiologic changes in chronic experimental pericarditis with effusion: semi-diagrammatic summary of data obtained on nine dogs (from Fishman and co-workers[25]). V. P., peripheral venous pressure; SCN, thiocyanate space; PL. VOL., plasma volume; A-V, arteriovenous oxygen difference in volumes per cent of oxygen; C.O., cardiac output; B. P., blood pressure (S, systolic and D, diastolic); R.P.F., renal plasma flow; G.F.R., glomerular filtration rate; Na excretion, sodium excretory rate in milliequivalents of sodium per minute, in response to an intravenous hypertonic saline load; (↑ Operation) day of operative placement of irritative cellophane bag about the heart, between visceral and parietal pericardial layers. Abscissa represents days postoperative to death (↑ Exitus). Discussed in text.

the sodium chloride and water excretion is dependent upon the glomerular filtration rate. Some years ago we put this to the test by producing pericarditis in the unanesthetized dog (fig. 7). By the use of irritating cellophane, an extensive pericarditis ensued and this led chronically to edema; this edema developed long before any change in resting cardiac output, blood pressure, renal blood flow, or glomerular filtration rate, but went, *pari passu*, with the elevation in venous pressure. It is difficult to believe that this could be produced by a "forward failure" mechanism which reduces the glomerular filtration rate and the renal plasma flow, and so presents the tubules with less water and less sodium chloride to excrete.

What does a reduction in renal plasma flow and in glomerular filtration rate do? This was studied recently by using renal artery constriction (fig. 8), recovery from temporary renal artery occlusion (fig. 9) and recovery from inferior vena cava occlusion above the liver which led to a reversible shock-like syndrome (fig. 10). In all instances the renal plasma flow and the glomerular filtration rate declined, yet the kidney recovered its ability to excrete sodium chloride and water before it overcame the constrictive or post-occlusive decline in blood flow and filtration

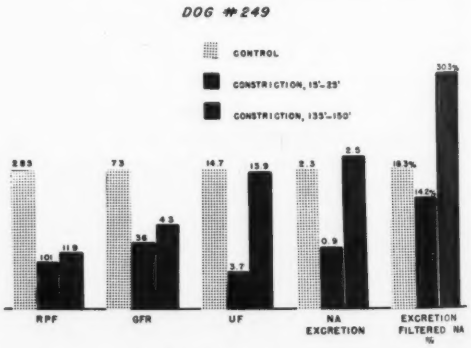

FIG. 8. Acute effect of bilateral renal artery constriction (from Stamler[37]). RPF, renal plasma flow cc. per minute; GFR, glomerular filtration rate, cc. per minute; UF, urine flow, cc. per minute; Na excretion, mEq. per minute. The numbers above the bars represent the numerical values in appropriate units.

rate. It is interesting and well known that the kidney has a protracted period of vasoconstriction following occlusion. The associated changes in renal salt and water exchanges are not due to irreversible damage to the tubules since histologic examinations fail to reveal any such changes, and furthermore, in animals allowed to survive, renal hemodynamics quickly returned to normal. All of these procedures were carried out on the unanesthetized trained dog and it has been the experience of this department that it is best to obtain these results in the unanesthetized animal.

It would follow from these observations that "forward failure," insofar as it reduces the flow through the kidney and its glomerular filtration rate, has no consistent influence on the excretion of sodium chloride or water. The body reacts to a sodium chloride load with a sodium chloride excretory response despite marked changes in the glomerular filtration rate and renal plasma flow. Yet in heart failure the body reacts as if the animal were sodium depleted (fig. 11), despite the fact that actually the animal is overloaded with sodium chloride and with water. Why?

In order to answer this question we have carried out a series of experiments on acute

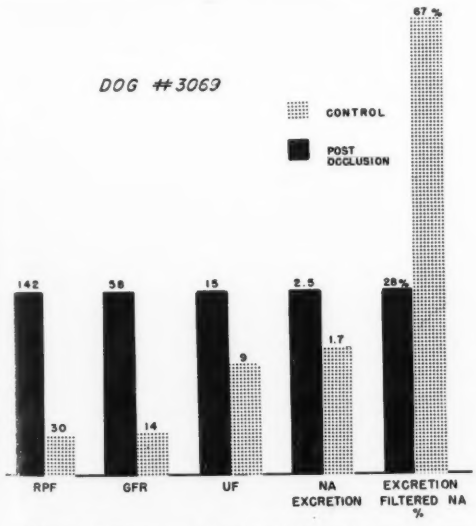

FIG. 9. Recovery following bilateral renal artery occlusion (from Stamler and associates[35]). Symbols as in figure 8.

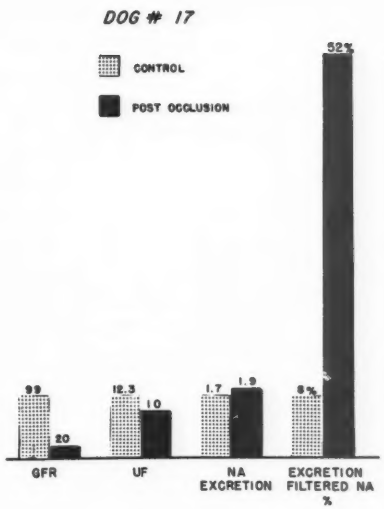

FIG. 10. Recovery following inferior vena cava occlusion above hepatic veins (from Stamler and associates[35]). Symbols as in figure 8.

and chronic vein occlusions. For example, when the inferior vena cava is partially occluded above the liver, the animal quickly develops ascites and this edema is sustained chronically. Associated with this there is sodium chloride and water retention (fig. 12). In contrast, when the inferior vena cava is constricted above the kidney, either acutely or chronically, no edema develops. In the acute experiments there is only a transient effect in the sense of water and sodium chloride retention (fig. 13). In the chronic experiments,

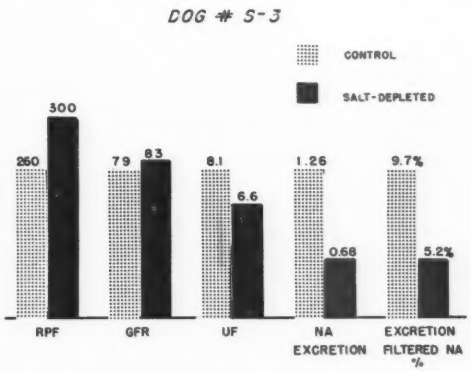

FIG. 11. Effects of chronic salt depletion (from Frieden and co-workers[29]). Symbols as in figure 8.

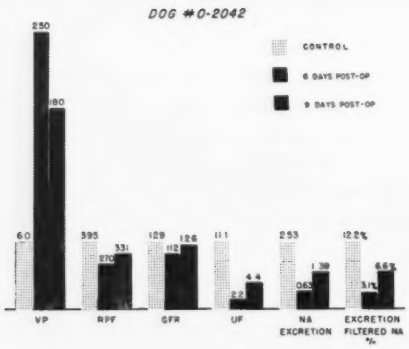

FIG. 12. Chronic effect of constriction of inferior vena cava above hepatic veins (from Stamler and colleagues[27]). VP, venous pressure, mm. water. Other symbols as in figure 8.

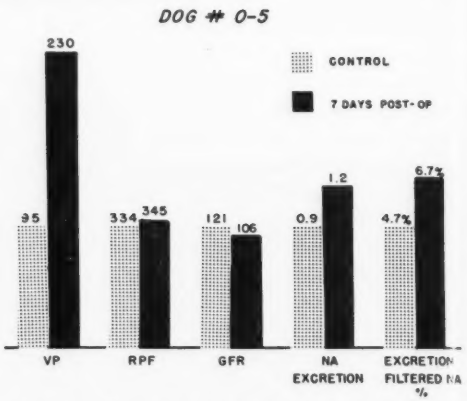

FIG. 14. Chronic effect of constriction of inferior vena cava above kidney (from Hwang and associates[30]). VP, venous pressure, mm. water. Other symbols as in figure 8.

no effect is observed (fig. 14). This leads to the conclusion that while transitory elevations of renal venous pressure can produce temporary declines in renal plasma flow and glomerular filtration rate, and associated retention of sodium chloride and water, this quickly disappears and is not seen in animals with chronic renal venous pressure rise, provided no edema ensues. Consequently, one can say that decreased renal sodium chloride and water excretion (with normal renal blood flow and glomerular filtration rate) occurring in association with the chronic ascites produced by narrowing of the inferior vena cava above the liver is not due to the elevated *renal* venous pressure which persists. On the other hand, inferior vena cava occlusion below the kidney does not lead to edema or to any change in water and sodium chloride excretion acutely or chronically, unless the femoral vein and epigastric vein are also occluded. Under these latter circumstances, edema will develop and sodium chloride and water retention will ensue (fig. 15). It is obvious from such experiments that it is not necessary to interfere with the circulation of the kidney, of the adrenals, or of the liver to produce edema, and, more particularly, to disturb the excretion of sodium chloride and water by the kidney.

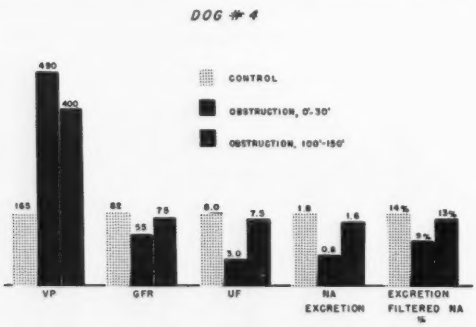

FIG. 13. Acute effects of obstruction of inferior vena cava above kidney (from Stamler and colleagues.[36]). VP, venous pressure, mm. water. Other symbols as in figure 8.

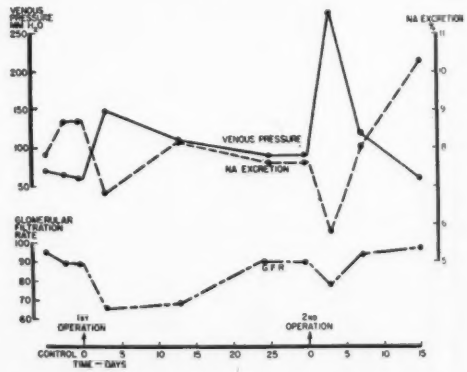

FIG. 15. Effect of elevated venous pressure in lower extremities on per cent Na excretion and glomerular filtration rate (from Frieden and co-workers[28]). First operation was ligation of inferior vena cava below the renal veins; second operation was ligation of femoral and inferior epigastric veins.

The possibility exists, of course, as has been claimed by others, that occlusion of the superior vena cava may have different effects. This we have tested. In acute experiments following such a procedure, neither edema nor any change in sodium chloride or water excretion occurred. In chronic experiments we have seen some animals develop edema (fig. 16) and others not. Those animals which developed edema behind the region of occlusion showed sodium chloride and water retention in the kidney. Those that did not showed no such effect. These experiments on the superior vena cava failed to reveal any evidence of any special volume receptors in the head—i.e., of receptors that would signal increased renal salt and water excretion as a result of cranial congestion. They failed to reveal that interference with the flow of blood to the hypothalamic and pituitary region has any extraordinary influence on sodium chloride and water excretion.

Finally, in some recent experiments in which mercurials were exhibited and found to inhibit sodium chloride absorption by the tubules, and in which sodium nitrate was substituted in part for the sodium chloride, the results suggested strongly that the mercurials operate primarily by interfering with the excretion of the chloride by the tubules, and that the changes in sodium, and presumably in water excretion, are secondary.

In reviewing our work on edema formation in congestion, we have come to the following conclusions: It is not stasis in any special area like the head, the kidney, the liver or the endocrines, per se, which causes sodium chloride and water dysfunction of the kidney, but it is stasis, per se, since stasis even in a region not involving such organs can lead to a similar disturbance. It is not clear from our work, or that reported in the literature, whether it is the local venous hypervolemia, or the elevated venous pressure, or the transudation, or the local changes in the tissues, or the tendency toward hypovolemia in the rest of the circulation when part of the blood is, so to speak, impounded, which is the trigger mechanism. However, the disturbance associated with rise of venous pressure in some fashion and independent of any special area sets up a receptor-effector mechanism that adjusts the kidney excretion of sodium chloride and water so that they are retained. This can readily be brought out when the body is loaded with a sodium chloride solution. We used 1.5 per cent sodium chloride or Ringer's solution at the perfusion rate of 6 to 10 cc. per minute. We do not know the location of the receptor, nor its character. We do not know whether hormonal factors are involved, nor do we understand the role of the central nervous system in this mechanism. Work is now being pursued in this department to try to get the answers to these questions. It is apparent from our work, however, that the mechanisms of sodium chloride and water disturbance operate in the tubules. It would appear that it is the reabsorption of sodium chloride and water that is affected, but it is possible that it may be in part an interference with actual secretion of sodium chloride and/or water from the blood into the tubules.

Edema in heart failure is caused by the heart, but the mechanism as outlined above involves a derangement of kidney function in which the kidney operates as if the body were depleted of sodium chloride and water despite the excess presence of both. In acute incompetence of the heart, the edema may be due in part to local transudation of fluid on a mechanical or reflexogenic basis, aided and

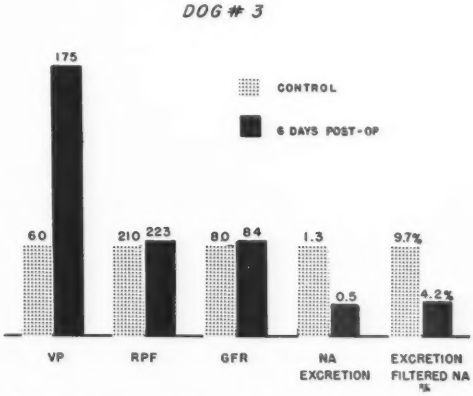

FIG. 16. Chronic effect of constriction of superior vena cava (from Frieden and co-workers[28]) VP, venous pressure, mm. water. Other symbols as in figure 8.

abetted by "forward failure" which alters renal blood flow and glomerular filtration rate, and by "backward failure" which, by elevation of renal venous pressure, has the same effect. This reduction in glomerular filtration rate may operate to interfere with the ability of the kidneys to excrete sodium chloride and water (glomerulotubular imbalance). However, the renal mechanism so set up is adjusted too quickly and in chronic failure is of little importance. Similarly, during periods of stress there is in the cardiac patient a greater decline in renal flow and in glomerular filtration rate, due to the development or exaggeration of "forward failure" or of renal venous congestion (leading to further glomerulotubular imbalances). This effect upon the kidney during periods of stress is only part of the picture because such stress leads to widespread venous congestion in other areas. If general venous congestion is in some fashion responsible for the derangement of tubular salt and water excretion during the resting state, then this effect would be exaggerated during periods of bodily stress.

In summary, we believe that heart failure sets up a receptor-effector system that results in a disturbance in the ability of the renal tubules to excrete sodium chloride and water so that edema ensues. This in some fashion is associated with the venous congestion.

Analyses of similar complex interlocking disturbances in body function other than those of water and sodium chloride exchanges would be of benefit in completing our understanding of the entire syndrome of heart failure. They would help to improve the knowledge by which rational management and therapy can be planned.

Conclusion

In conclusion, you can see that the problem of cardiac failure is not a simple one as at first sight it might appear to be, and that its complexity is only now beginning to be appreciated. I predict that in the future our understanding will bring light upon the obscure relationships. At any rate you will admit that the functional viewpoints expressed concerning cardiac failure point to the direction from which illumination will come.

BIBLIOGRAPHY

Bibliography selected from the work of the author and his associates, upon which this lecture is based.

[1] Wiggers, C. J., and Katz, L. N.: The selective effect of the accelerator nerves on ventricular systole. Proc. Soc. Exper. Biol. & Med. **17:** 94, 1920.

[2] —, and —: The contour of the ventricular volume curves under different conditions. Am. J. Physiol. **58:** 439, 1922.

[3] Katz, L. N.: Observations on the dynamics of ventricular contraction in the heart-lung preparation. Am. J. Physiol. **80:** 470, 1927.

[4] —: The relation of initial volume and initial pressure to the dynamics of the ventricular contraction. Am. J. Physiol. **87:** 348, 1928.

[5] —: The role played by the ventricular relaxation process in filling the ventricle. Am. J. Physiol. **95:** 542, 1930.

[6] Brams, W. A., and Katz, L. N.: Studies on the over-distended heart. I. Effects of venesection. Am. J. Physiol. **98:** 556, 1931.

[7] Katz, L. N., and Brams, W. A.: Studies on the overdistended heart. II. The role of relaxation in filling the distended and overdistended heart. Am. J. Physiol. **98:** 569, 1931.

[8] —: Observations on the external work of the isolated turtle heart. Am. J. Physiol. **99:** 579, 1932.

[9] Soskin, S., and Katz, L. N.: Observations on the sugar metabolism of the isolated heart. Proc. XIV Intern. Cong. of Physiol., Rome, August-Sept., 1932. Arch. sc. biol. **18:** 321, 1933.

[10] Johnson, V., and Katz, L. N.: Tone in the mammalian ventricle. Am. J. Physiol. **118:** 26, 1937.

[11] Katz, L. N., and Mendlowitz, M.: Heart failure analyzed in the isolated heart circuit. Am. J. Physiol. **122:** 262, 1938.

[12] —, —, and Kaplan, H. A.: The action of digitalis on the isolated heart. Am. Heart J. **16:** 149, 1938.

[13] —: Observations on cardiac failure and the mode of its production. Am. A. Advancement of Science. No. 13, 184, 1940.

[14] —, Jochim, K., Lindner, E., and Landowne, M.: The Effect of Varying Resistance-Load and Input-Load on the Energetics of the Surviving Mammalian Heart. Am. J. Physiol. **134:** 636, 1941.

[15] —: Mechanism of heart failure. J. Mt. Sinai Hospital **8:** 668, 1942.

[16] Landowne, M., and Katz, L. N.: Heart: work and failure. In Medical Physics. Chicago, Year Book Publishers, 1944. P. 578.

[17] KATZ, L. N., WISE, W., AND JOCHIM, K.: The dynamics of the isolated heart and heart-lung preparations of the dog. Am. J. Physiol. **143:** 463, 1945.

[18] —, —, AND —: The dynamics of the non-failure period of the isolated heart and heart-lung preparation. Am. J. Physiol. **143:** 495, 1945.

[19] —, —, AND —: The dynamic alterations in heart failure in the isolated heart and heart-lung preparation. Am. J. Physiol. **143:** 507, 1945.

[20] —: The Dynamics of Heart Failure. Jubilee of Instituto Nacional de Cardiologia, Liber Homenaje el Professor Doctor Ignacio Chavez, Universidad Nacional Automona Mexico, 1945.

[21] WISE, W., MEYER, J., KATZ, L. N., LENDRUM, B., AND JOCHIM, K.: The oxygen consumption and mechanical efficiency of the heart before and during heart failure. Am. J. Physiol. **147:** 28, 1946.

[22] SURTSHIN, A., KATZ, L. N., AND RODBARD, S.: An attempt to produce pulmonary edema by increased intracranial pressure. Am. J. Physiol. **152:** 589, 1948.

[23] PREC, O., KATZ, L. N., SENNETT, L., ROSENMAN, R. H., FISHMAN, A. P., AND HWANG, W.: Determination of kinetic energy of the heart in man. Am. J. Physiol. **159:** 483, 1949.

[24] LANDOWNE, M., AND KATZ, L. N.: Circulatory system: Heart: work and failure. In Medical Physics. Chicago, Year Book Publishers, 1950. Vol. 2, p. 194.

[25] FISHMAN, A. P., STAMLER, J., KATZ, L. N., MILLER, A. J., SILBER, E. N., AND RUBENSTEIN, L.: Mechanisms of edema formation in chronic experimental pericarditis with effusion. J. Clin. Investigation **29:** 521, 1950.

[26] HWANG, W., AKMAN, L. C., MILLER, A. J., SILBER, E. N., STAMLER, J., AND KATZ, L. N.: Effects of sustained elevation of renal venous pressure on sodium excretion in unanesthetized dog. Am. J. Physiol. **162:** 649, 1950.

[27] STAMLER, J., GOLDBERG, H., GORDON, A., WEINSHEL, M., AND KATZ, L. N.: Relationship of elevated renal venous pressure to sodium clearances and edema formation in unanesthetized dogs. Am. J. Physiol. **166:** 400, 1951.

[28] FRIEDEN, J., RICE, L., ELISBERG, E. I., EISENSTEIN, B., AND KATZ, L. N.: Effects of chronic peripheral venous congestion on renal sodium excretion. Am. J. Physiol. **168:** 650, 1952.

[29] —, —, AND —: Renal tubular sodium metabolism in sodium deficiency states. Am. J. Physiol. **168:** 93, 1952.

[30] RICE, L., FRIEDEN, J., KATZ, L. N., ELISBERG, E. I., AND ROSENBERG, E.: A case of spontaneous thrombosis of the superior vena cava with some observations on the mechanism of edema formation. Am. Heart J. **43:** 821, 1952.

[31] KATZ, L. N., AND STAMLER, J.: Venous pressure, renal function and edema formation. Cardiologia **21:** 307, 1952.

[32] RICE, L., FRIEDEN, J., KAPLAN, B. M., AND SMITH, M.: Tubular action of mercurial diuretics. Am. J. Physiol. **175:** 47, 1953.

[33] —, —, —, AND—: Renal tubular resistance to mercurial action in sodium deficiency. Am. J. Physiol. **175:** 45, 1953.

[34] RODBARD, S., GRAHAM, G. R., AND WILLIAMS, F.: Continuous and simultaneous measurement of total coronary flow, venous return and cardiac output in the dog. J. Applied Physiol. **6:** 311, 1953.

[35] STAMLER, J., GOLD, H., CARNOW, B. W., AND RICE, L.: "Forward failure" and "backward failure" hemodynamic influences on renal sodium exchanges in unanesthetized, salt-loaded dogs. Proc., XIX Int'l Physiol. Congress, p. 792, 1953.

[36] —, CARNOW, B. W., GOLD, H., AND RICE, L.: The effect of an acute venous pressure elevation on plasma volume, kidney function and sodium excretion in the unanesthetized dog. Proc., Scientific Sessions, 26th Annual Meeting Am. Heart A., p. 93, 1953.

[37] —: Acute effects of constriction of renal arteries on renal sodium exchanges in unanesthetized dogs. Federation Proc. **12:** 137, 1953.

[38] KATZ, A. M., KATZ, L. N., AND WILLIAMS, F. L.: Regulation of coronary flow. Federation Proc. **13:** 77, 1954.

[39] KATZ, L. N., KATZ, A. M., AND WILLIAMS, F.: Observations on cardiac metabolic adjustments to alterations in work performance. Federation Proc. **13:** 78, 1954.

Marcumar [3-(1′-phenyl-propyl)-4-hydroxy-coumarin]. A New Anticoagulant

By René Bourgain, M.D., Margaret Todd, B.S., Lorraine Herzig, B.A., and Irving S. Wright, M.D.

Marcumar [3-(1′-phenyl-propyl)-4-hydroxycoumarin] is a new anticoagulant. Marcumar acts more rapidly than Dicumarol, but not quite as rapidly as Tromexan. The action is more prolonged than Dicumarol. As with other anticoagulants, the administration of Marcumar requires conscientious observation and accurate prothrombin complex determinations.

In the last two decades the use of anticoagulant therapy for thromboembolic disorders has become generally accepted. The hypoprothrombinemic action of certain coumarin derivatives made these drugs valuable anticoagulants. However, Dicumarol (3-3′-methylenebis-4-hydroxycoumarin) and Tromexan (3, 3′-carboxymethylenebis-4-hydroxycoumarin ethyl ester), although frequently prescribed, have their disadvantages. The prolonged delay before anticoagulant activity can be detected with the former and the rapidly disappearing effect on the blood clotting mechanism of the latter stimulated research with other coumarin derivatives. In recent years efforts were directed to the synthesis of an anticoagulant with a short latent period following administration and a moderate cumulative effect, thus facilitating control. In the last year anticoagulant properties of a compound called Marcumar [3-(1′-phenyl-propyl)-4-hydroxycoumarin] were described by Koller and Jakob[1] and Jürgens.[2] On equal weight basis these investigators observed a higher anticoagulant activity for Marcumar than Dicumarol, and described an antagonistic effect of vitamin K_1 for this new drug. Matis,[3] Hartert and Hartert,[4] Thies,[5] and De Nicola and co-workers[6] confirmed these observations independently. The action of Marcumar on the dilute and undilute prothrombin complex time, proconvertin time, and prothrombin time after oral and intravenous administration to rabbits and after oral administration to humans are described herein.

Methods and Materials

Prothrombin complex time* determinations were done by the Link-Shapiro[7] modification of Quick's one-stage method on undiluted and diluted plasma (12.5 per cent in normal saline). A prolonged dilute prothrombin complex time (D.P.C.T.) or undilute prothrombin complex time (U.P.C.T.) may be due to a decrease in proconvertin or prothrombin or both.

Proconvertin times were performed by the method described by Owren.[8]

The determination of the prothrombin level was done by adding 0.1 ml. of a mixture of equal amounts of stored serum and plasma treated with barium carbonate to 0.1 ml. of the diluted plasma to be examined (10 per cent in normal saline). The clotting time obtained after addition of calcium-thromboplastin to this mixture reflects exclusively the activity of the prothrombin.

The thromboplastin used in the above-mentioned determinations was prepared in our laboratory from dried rabbit lung. The calcium chloride used was a 0.025 molar solution.

As rabbits manifest important differences in sensitivity to coumarin derivatives after oral administration, only animals which develop a dilute prothrombin time of 60 seconds or more for at least one day after oral administration of 2.5 mg. Dicumarol were accepted for study with Marcumar.

Results

Control studies on normal rabbit plasma were done in 60 animals. The average values ob-

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* Since the methods of Quick and Link-Shapiro measure a complex substance of which proconvertin and prothrombin are important factors, the term *complex* will be used to differentiate this mixture from determinations of prothrombin alone.

TABLE 1.—*Control Values for the Undilute (U.P.C.T.) and Dilute Prothrombin Complex Times (D.P.C.T.), Proconvertin Time and Prothrombin Time of Rabbit Plasma (60 Animals)*

	Avg. (sec.)	Range (sec.)	S. D. (sec.)
U.P.C.T.	8.5	7.2–9.7	±0.7
D.P.C.T.	22.3	20.0–28.0	±2.7
Proconvertin time	22.9	18.5–27.4	±2.2
Prothrombin time	14.0	10.2–16.1	±1.9

served for the undilute and the dilute prothrombin complex times, the proconvertin time and the prothrombin time are shown in table 1.

A single dose of 2.5 mg. Marcumar per kilogram of body weight was administered orally to 11 animals after 48 hours starvation. Food was withheld for five more days. Evidence of anticoagulant activity was detected 12 hours after administration. At that time the proconvertin time was prolonged (average, 47 seconds), but this hypoconvertinemia was not sufficient to prolong the dilute or undilute prothrombin complex times significantly. The dilute and undilute prothrombin complex times became prolonged after 18 hours, and reached a maximum value on the second day after the administration of the drug. The curve observed for the proconvertin time is similar to the curve observed for the undilute and dilute prothrombin complex times. The prothrombin, however, was decreased between 18 and 24 hours and maximal decreases were observed between the second and third day. The activity evidenced by a prolongation of the

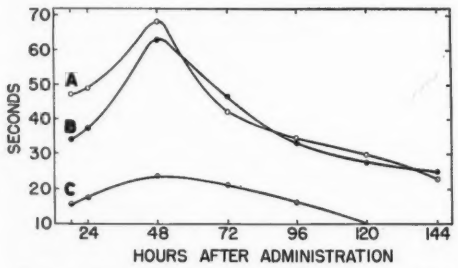

FIG. 1. Curves of average values for the dilute prothrombin complex time (*B*), the proconvertin time (*A*) and the prothrombin time (*C*) in 11 rabbits after oral administration of 2.5 mg. Marcumar per kilogram.

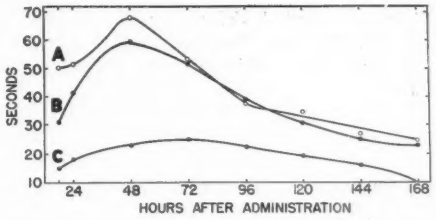

FIG. 2. Curves of average values for the dilute prothrombin complex time (*B*), the proconvertin time (*A*) and the prothrombin time (*C*) in 10 rabbits after oral administration of 4 mg. Marcumar per kilogram.

undilute and dilute prothrombin complex times lasted from four to five days.

Under the same experimental conditions 4 mg. of Marcumar per kilogram were given orally to 10 animals, and 10 mg. of Marcumar per kilogram were given to four animals. Similar findings were observed as after the oral dose of 2.5 mg. of Marcumar per kilogram. In both groups the peak of anticoagulant activity occurred after two days and the effect disappeared on the fifth day as evidenced by the dilute prothrombin complex time.

To two rabbits 10 mg. of Marcumar were given intravenously. The dilute prothrombin complex times reached a peak two days later (69.2 seconds in one and 35.4 seconds in the other animal). The dilute complex time was normal after five days in the first and after four days in the other animal. The proconvertin times followed a curve similar to the dilute prothrombin complex times. The prothrombin, however, reached a minimum level between two and three days after injection.

A daily oral dose of 4 mg. of Marcumar per kilogram was given to three rabbits on normal diet. In one animal the dilute prothrombin complex time was 139.5 seconds 11 days after the initial dose, and remained at 90 seconds for six days, at which time the drug was discontinued. In a second rabbit the dilute complex time was greater than five minutes after eight days. Marcumar was then withheld. In a third animal the dilute complex time was 94.2 seconds after eight days, and remained at this level for three days. The dilute complex time became normal within 48 hours after Marcumar was discontinued in the three animals.

TABLE 2.—*Control Values for the Undilute and Dilute Prothrombin Complex Times, Proconvertin Time, and Prothrombin Time of Normal Human Plasma*

	Avg. (sec.)	Range (sec.)	S. D. (sec.)
U.P.C.T.	14.8	13.0–15.6	±1.02
D.P.C.T.	38.1	36.2–41.0	±2.64
Proconvertin time	28.7	25.6–30.1	±1.98
Prothrombin time	20.9	19.5–22.3	±0.05

One rabbit was given a daily dose of 5 mg. of Marcumar per kilogram. This animal expired 11 days later at which time the dilute prothrombin complex time was greater than five minutes, and had been greater than 150 seconds for the last six days. On autopsy, extensive hemorrhages were found in the chest cavity and the large bowel. However, no visible renal hemorrhages were observed.

A single oral dose of 4 mg. of Marcumar per kilogram was given to two rabbits on normal diet, and a prolonged dilute prothrombin complex time was observed for two days.

CLINICAL STUDIES

The control values observed on normal human plasma of 40 healthy individuals for the undilute and dilute prothrombin complex times, proconvertin time and prothrombin time are shown in table 2.

A single oral dose of 18 mg. Marcumar was given to nine patients. Evidence of anticoagulant activity was detected 24 hours after administration (fig. 3). The maximum value for the undilute and dilute prothrombin complex times occurred on the third day. At that time the average dilute time was 60 seconds. A normal dilute prothrombin time was observed on the fifth day. The peak of the proconvertin time occurred 12 to 24 hours earlier than the peak of the dilute time. Maximal decrease in prothrombin was noticed after four days (24 hours after the peak of the dilute complex time).

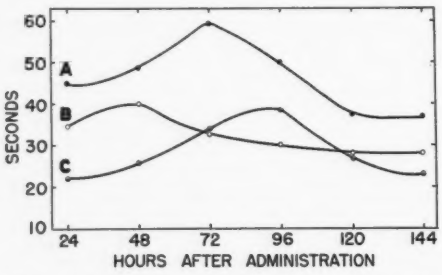

FIG. 3. Curves of average values for the dilute prothrombin complex time (*A*), the proconvertin time (*B*) and the prothrombin time (*C*) in nine patients after oral administration of 18 mg. Marcumar.

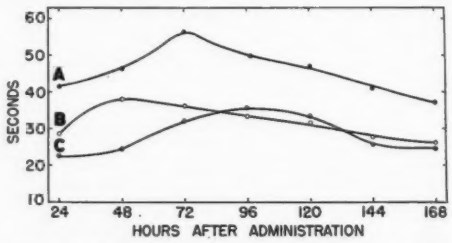

FIG. 4. Curves of average values for the dilute prothrombin complex time (*A*), the proconvertin time (*B*) and the prothrombin time (*C*) in seven patients after oral administration of 21 mg. Marcumar.

A single oral dose of 21 mg. Marcumar was given to seven patients. The undilute and dilute prothrombin complex times, proconvertin time, and prothrombin time were in the range of the values observed after administration of 18 mg. Marcumar. The activity lasted slightly longer; the dilute time became normal on the sixth day after administration.

Anticoagulant treatment with Marcumar was given to several patients suffering from thromboembolic diseases. After an initial dosage of 21 mg. the first day and 9 mg. the

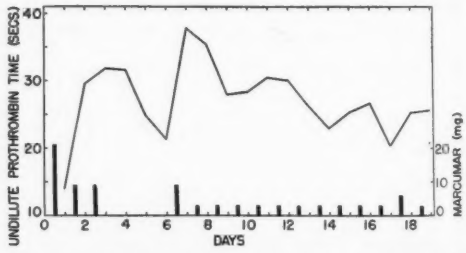

FIG. 5. Evolution of the undilute prothrombin complex time in a patient suffering from thrombophlebitis and treated with Marcumar. The first day 21 mg. was given, the second and third day 9 mg., after which the drug was discontinued for three days. The administration of 9 mg. the sixth day and 3 mg. daily subsequently allowed us to keep the undilute prothrombin time within the therapeutic range.

second day, the treatment was continued by giving 3 mg. of Marcumar daily. Under these conditions, the undilute prothrombin complex time varied between 22 and 35 seconds, and the dilute time between 80 and 120 seconds. One patient received 9 mg. of Marcumar on the third day by mistake, after which the treatment was continued as indicated in figure 5. Another patient had an undilute complex time of 71 seconds and a dilute time of more than three minutes eight days after treatment was started. The administration of 100 mg. of vitamin K_1 (orally) reduced the undilute time to 52 seconds within four hours. The next day the undilute and the dilute prothrombin complex times were normal.

Discussion

The experimental and clinical studies demonstrate and anticoagulant properties of Marcumar. Pharmacologically this drug acts by depressing both the proconvertin and the prothrombin in the plasma.

After oral or intravenous administration of Marcumar to rabbits, proconvertin is the first factor affected. The decrease of this factor can be detected usually within 12 hours after administration. The undilute and dilute prothrombin complex times, however, do not show any change before 18 hours. The peaks of the proconvertin time, and undilute and dilute complex times occur simultaneously after 48 hours. Maximal decrease in prothrombin is observed between 48 and 72 hours. Between the peak of the proconvertin time and the prothrombin time there is a 12- to 24-hour delay. The anticoagulant effect lasts between four and five days when the dosage is equal to or greater than 2.5 mg. per kilogram. Identical rates of activity are observed when Marcumar is given in dosages from 2.5 mg. per kilogram to 10 mg. per kilogram. Similar findings were observed by Overman[9] for Dicumarol after oral administration of dosages greater than 6 mg. However, Dicumarol in doses from 2.5 mg. to 6 mg. gave a proportional rise in the dilute prothrombin complex time. This proportional increase of the dilute time was not observed with Marcumar when increasing amounts of this drug are given.

It is well known that rabbits on normal diet actively synthesize vitamin K in the intestine. The duration of anticoagulant activity after oral administration of 2.5 mg. of Marcumar per kilogram is five days when the animal is starved, but is reduced to three days when the rabbit is on normal diet. Under the same conditions the anticoagulant activity of Marcumar after intravenous injection of 10 mg. is reduced from four days to one day. These findings suggest the antagonistic effect of vitamin K on the anticoagulant activity of Marcumar.

The oral administration of 18 mg. of Marcumar to humans results in prolonged dilute and undilute prothrombin complex times, a maximum being reached on the third day after administration. On the fifth day normal values are observed. Similar results are found after administration of 21 mg. of Marcumar except for a more prolonged duration of action. The prothrombin complex time determined by the dilute method returns to normal on the sixth day. The proconvertin time is prolonged within 18 hours, reaching a peak after two days. The prothrombin presents a maximal decrease between the third and fourth day. The peaks of the undilute and the dilute complex times occur on the third day. The anticoagulant activity evidenced by prolonged undilute and dilute prothrombin complex times lasts four to five days. These findings demonstrate and confirm the prolonged duration of activity related to Marcumar.

The administration of 3 mg. Marcumar daily after the initial dose of 21 mg. on the first day and 9 mg. on the second day usually keeps the dilute and undilute prothrombin complex times within the limits of therapeutic value. (The time by the undilute method is between 20 and 35 seconds, by the dilute method between 70 and 160 seconds.) Compared with Dicumarol, Marcumar is much more active in humans. In patients, the daily dosage required after stabilization of the dilute and undilute complex times in the therapeutic range is equal to or smaller than 3 mg. This means an average activity 20 times that of Dicumarol. Marcumar is a more rapidly acting drug than Dicumarol, but it is frequently not as rapid as Tromexan. Evidence of antico-

agulant activity can usually be detected between 18 and 24 hours after administration.

Summary

Marcumar [3-(1′-phenyl-propyl)-4-hydroxycoumarin] is a new anticoagulant. It has been studied in animals and in humans subjects. It is suitable and effective for anticoagulant therapy. Anticoagulant activity can be detected for four to five days in rabbits after one single oral dose of 2.5 mg. per kilogram, and for five days in humans after one single dose of 18 mg. The administration of higher doses to rabbits gives a response similar to that produced by 2.5 mg. per kilogram. However, in humans the increase in dosage seems to prolong slightly the duration of activity. In patients the therapeutic optimum can be obtained when 21 mg. Marcumar is given the first day and 9 mg. the second day. The administration of 3 mg. daily usually keeps the undilute prothrombin complex time and dilute prothrombin complex time within the therapeutic range. The dosage requirements vary between patients, and in the same patient from day to day. There is also a tendency for the effect to accumulate over a period of time on the same dosage. As with all other coumarins, conscientious observation and frequent checking of the undilute prothrombin complex time and dilute prothrombin complex time are essential to safe therapy.

Sumario Español

Marcumar [3-(1′-phenyl-propyl)-4-hydroxycoumarin] es un nuevo anticoagulante. Se ha estudiado en animales y sujetos humanos. Es apropiado y efectivo en la terapia anticoagulante. Actividad anticoagulante se puede percibir por cuatro o cinco días en conejos luego de una sencilla dosis de 2.5 mg. por kilogramo y por cinco días en el humano luego de una dosis de 18 mg. La administración de dosis mayores a conejos produce una repuesta similar a la producida por 2.5 mg. por kilogramo. Sinembargo, en humanos el aumento en dosis parece prolongar ligeramente la duración de actividad. En pacientes, el óptimo terapéutico se puede obtener cuando 21 mg. de Marcumar se administran el primer día y 9 mg. el segundo día. La administración de 3 mg. diarios usualmente mantiene el tiempo del complejo de protrombina no diluído y el tiempo del complejo de protrombina diluído entre el margen terapéutico. Los requerimientos en dosis varían entre pacientes y en el mismo paciente de día en día. También hay una tendencia en el efecto de ser cumulativo luego de un período de tiempo con la misma dosis. Como con todos los otros coumarins, observación concienzuda y una verificación frecuente del tiempo del complejo de protrombina no diluído y del tiempo del complejo de protrombina diluído son esenciales para la terapia sin peligro.

Acknowledgments

Acknowledgment is made to Dr. Leo A. Pirk of Hoffmann-LaRoche, Inc., Nutley, N. J., for supplies of Marcumar.

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REFERENCES

1. Koller, F., and Jakob, H.: Über ein neues, hochaktives Antikoagulans mit protrahierter Wirkung (Marcoumar). Schweiz. med. Wchnschr. **83:** 476, 1953.
2. Jürgens, R.: Experimentelle Untersuchungen uber das Antikoagulans Marcoumar [3-(1′-phenyl-propyl)-4-oxy-cumarin] und seinen Antagonisten Konakion [synthetisches Vitamin K_1] Schweiz. med. Wchnschr. **83:** 471, 1953.
3. Matis, P.: Marcumar [3-(1′-phenyl-propyl)-4-oxy-cumarin], ein neues Superdicumarol. Ärztl. Forsch. **7:** 298, 1953.
4. Hartert, H., and Hartert, I.: Klinische Erfahrungen mit einem neuen hochwirksamen Dicumarolderivat. Klin. Wchnschr. **31:** 852, 1953.
5. Thies, H. A.: Die antithrombotische Bedeutung eines neuartigen Cumarinderivats (Marcumar). Medizinische, pp. 1434–1435, Oct. 31, 1953.
6. De Nicola, P., Colli, A., and Rosti, P.: Terapia anticoagulante con preparati ad azione dicumarinica prolungata [3-(1′-fenil-propil)-4-ossicumarina]. Azione antidotica della vitamina K_1 sintetica. Haematologica **37:** 1953.
7. Shapiro, S.: Hyperprothrombinemia, a premonitory sign of thromboembolization (description of a method). Exper. Med. & Surg. **2:** 103, 1944.
8. Owren, P. A.: Proconvertin, new clotting factor. Scandinav. J. Clin. & Lab. Invest. **3:** 168, 1951.
9. Overman, R. S., Stahmann, M. A., Sullivan, W. R., Huebner, C. F., Campbell, H. A., and Link, K. P.: Studies on the hemorrhagic sweet clover disease. VII. The effect of 3,3′-methylenebis (4-hydroxycoumarin) on the prothrombin time of the plasma of various animals. J. Biol. Chem. **142:** 941, 1942.

Clinical Experience with Dipaxin and with the Combined Use of Prothrombopenic Agents

By Ricardo Katz, M.D., Héctor Ducci, M.D., Werner Roeschmann, M.D., and Lucía Toriello, M.D.

The experience with a new prothrombopenic agent, Dipaxin, is presented. With a 30 mg. dose a prothrombin complex concentration under 30 per cent is reached in 41 hours or less. When associated with 1500 mg. of Tromexan the latent period is reduced to 24 hours. The prothrombopenic action of Dipaxin is readily counteracted with vitamin K_1 administered either orally or intravenously.

ANTICOAGULANT therapy has its main indication during the acute phase of thromboembolic disease. Among the drugs with anticoagulant properties the most commonly used are those which interfere with the synthesis of prothrombin and stable factor, the so-called prothrombopenic agents.

We have had a large personal experience with bishydroxycoumarin (Dicumarol), ethyl biscoumacetate (Tromexan), cyclocumarol (Cumopyran) and phenindione (Danilone). From these, we consider Danilone the drug of choice as its action starts in a relatively short time (36 to 48 hours) and the initial and maintenance doses are very similar in different individuals.[1]

Many efforts have been directed towards the finding of a prothrombopenic agent with a quicker action and a more reproducible dosage. We have studied a new indandione derivative the 2-diphenylacetyl-1,3-indandione (Dipaxin) which appears to meet the above mentioned characteristics and are presenting in this paper our observations.

Drugs used in this study were made available through the courtesy of Abbott Laboratories, North Chicago, Ill., (Dicumarol and Cumopyran); J. R. Geigy, Basel, Switzerland (Tromexan), Charles E. Frosst and Co., Montreal, Canada (Danilone), Dr. H. F. Hailman from the Upjohn Co., Kalamazoo, Mich. (Dipaxin), Hoffmann-La Roche, Basel, Switzerland (Synkavit and Konakion), and Merck and Co. Inc., Rahway, N. J. (Mephyton).

From the Department of Medicine (Dr. H. Alessandri), University of Chile Medical School, Hospital del Salvador, Santiago, Chile.

Correll and co-workers[2] have reported that out of a group of compounds including Dicumarol, Tromexan and 17 analogs of the indandione group, Dipaxin has the greatest prothrombopenic action on rabbits. Field and associates[3] and Duff and colleagues[4] have administered Dipaxin to human subjects without observing any toxic effects. They consider this drug more potent than any other oral anticoagulant with which they have had experience. The former workers recommended an initial dose of 30 mg. and the latter a dose of between 30 to 75 mg. From their study on the use of Dipaxin in 80 patients, Pascale and Olwin[5] concluded that it is an effective prothrombin depressant serving to reduce this coagulation factor to an effective therapeutic level in 48 to 60 hours.

The structure of Dipaxin is shown in figure 1.

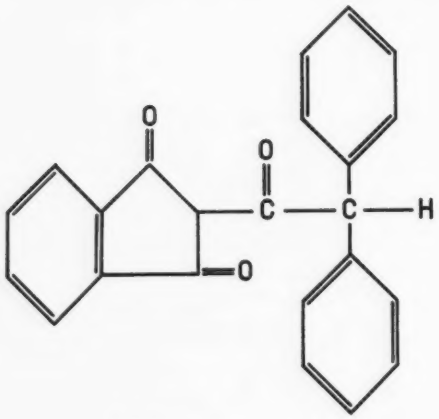
Methods

Blood prothrombin complex concentration was measured according to the one-stage method of Quick.[6] In some instances the procedure of Owren[7] was used to measure the activity of prothrombin and stable factor (proconvertin) and of both factors combined. Labile factor was determined by Stefanini's method.[8] Human brain thromboplastin prepared according to Owren was used throughout.

Study and Results

Effect of a Single Dose of Dipaxin

The action of a single dose of 30 mg. of Dipaxin administered orally was studied in 10 individuals who did not present any liver,



$C_{23}H_{16}O_3$

2-diphenylacetyl - 1,3 - indandione

FIG. 1. The structure of Dipaxin.

kidney or hematological disturbance. These results are shown in figure 2.

It can be observed easily that the action of Dipaxin on the prothrombin complex* is already evident at the seventeenth hour. At the twenty-fourth hour, 5 out of 10 subjects showed a prothrombin complex concentration below 30 per cent, that is to say a useful therapeutic level. In the remaining five the values were between 32 and 44 per cent. At the forty first hour all the controls showed useful prothrombin complex levels between 8 and 28 per cent, which lasted for about 100 hours. A quicker effect could not be obtained by increasing the dose up to 40 mg.

Comparison of Dipaxin with Danilone and Tromexan

The effect of a single dose of Dipaxin compared favorably with that of an equivalent single dose of Danilone. After 300 mg. of the latter none of the 10 subjects studied showed a prothrombin complex concentration below 30 per cent at the twenty fourth hour, and only in eight was this level obtained by the thirty sixth hour. In the remaining two this level was never obtained (fig. 3).

When the prothrombopenic actions of

* Prothrombin complex concentration applies to the values obtained by the method of Quick.

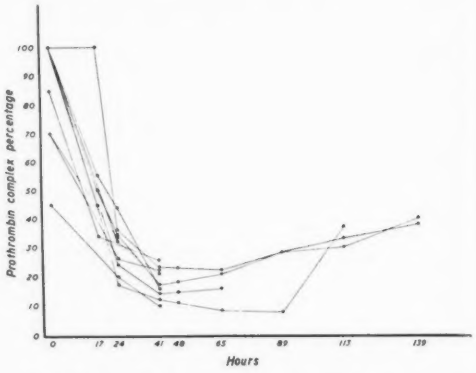


FIG. 2. Effect of a single 30 mg. dose of Dipaxin administered orally on the prothrombin complex concentration in 10 individuals.

Dipaxin and Tromexan are compared, the results are very similar although the latter shows a slightly faster effect. This is demonstrated in the five illustrative examples shown in figure 4. All these cases had a prothrombin complex concentration below 34 per cent 24 hours after a single dose of 1500 mg. of Tromexan.

Effect of Sodium Menadiol Diphosphate (Synkavit) and Fitilmenadione (Vitamin K_1) on the Hypoprothrombinemia Induced by Dipaxin

Two patients under treatment with Dipaxin in whom the prothrombin complex had been reduced below 25 per cent, received 30 mg. of

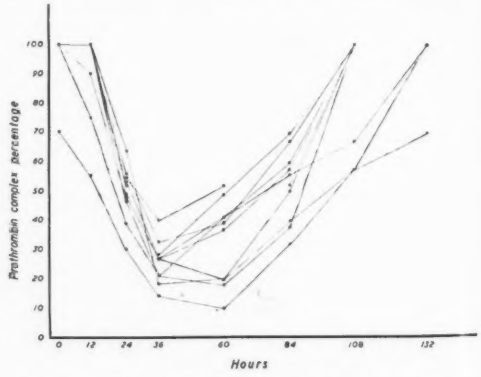


FIG. 3. Effect of a single 300 mg. dose of Danilone, administered orally, on the prothrombin complex concentration in 10 individuals.

Synkavit intravenously, with no demonstrable effect on the prothrombin complex during the following 24 hours (fig. 5). This may appear to be too low a dose but the same lack of response was observed by Pascale and Olwin[5] with much larger doses. In one patient the last dose of Dipaxin had been given 36 hours before the Synkavit injection and in the other, 42 hours before.

Two other patients under treatment with Dipaxin in whom the prothrombin complex had been reduced below 25 per cent, received 50 mg. of vitamin K_1 (Mephyton) intravenously. The prothrombin complex values rose significantly during the following hours being above 45 per cent at the fourth hour and reaching the pretreatment values in 24 hours. In one patient the last dose of Dipaxin had been given 17 hours before the vitamin K_1 injection and in the other 42 hours before (fig. 5). Such high intravenous doses of Mephyton have the serious drawback of conditioning a refractory period during which the patient does not respond to new doses of the prothrombopenic agent.[9] Occasionally a dangerous prothrombin complex level occurs during treatment with Dipaxin as with other prothrombopenic drugs. It is our experience that under these circumstances, the administration of a small dose (3 to 5 mg.) of vitamin K_1 (Konakion) by mouth rapidly brings the prothrombin complex to safe values without rendering the patient refractory to the continuation of treatment.

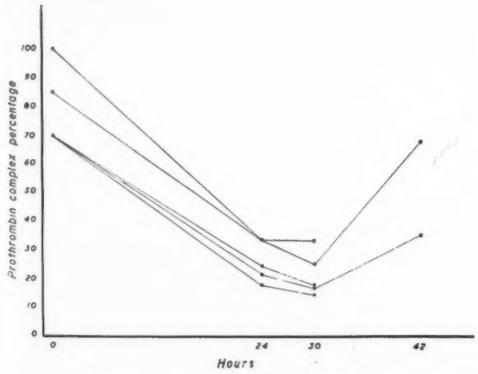


FIG. 4. Effect of a single 1500 mg. dose of Tromexan, administered orally, on the prothrombin complex concentration in five individuals.

Use of Dipaxin in Thromboembolic Disease

Dipaxin has been used in 60 cases of thromboembolic disease. An initial dose of 30 mg. was administered and all the cases showed a prothrombin complex concentration below 30 per cent on the second day. The maintenance dosage depends on the patients' individual reaction to the drug, but it is fairly constant and it fluctuates between 3 and 5 mg. per day. Only 14 per cent of our cases under prolonged treatment presented in some of the determinations prothrombin complex concentrations above 35 per cent. This figure is similar to the one reported by us for Danilone (16 per cent) and better than those for Dicumarol (30 per cent) and Tromexan (53 per cent).[10] Transient hematuria was the only hemorrhagic episode in this series (1.7 per cent).

According to our experience, the anticoagulant treatment of thromboembolic disease with Dipaxin has the same beneficial effects as Dicumarol, Danilone and Tromexan.

Effect of Dipaxin on the Components of the Prothrombin Complex

No depression of the concentration of the labile factor was observed in any of the patients treated with Dipaxin in whom this component was determined. This lack of effect on the labile factor has been also observed for Dicumarol,[11] Tromexan[12] and Danilone.[1]

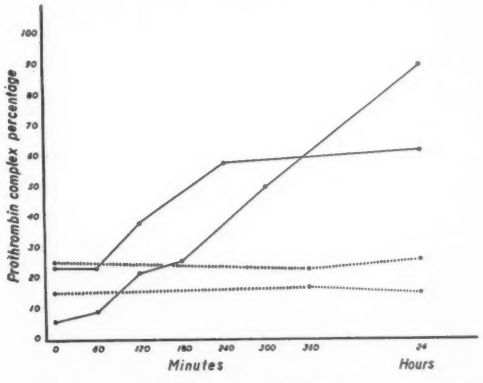


FIG. 5. Effect of a 30 mg. dose of sodium menadiol diphosphate (Synkavit), dotted line, and a 50 mg. dose of fitilmenadione (vitamin K_1), solid line, administered intravenously on the hypoprothrombinemia induced by Dipaxin.

The concentration of prothrombin, of stable factor (proconvertin), and of prothrombin and stable factor (proconvertin) combined was also measured in all 60 patients under treatment with Dipaxin for thromboembolic disease. The behavior of these factors was similar to that observed during treatment with other prothrombopenic drugs.[12] In most patients stable factor is definitely depressed, reaching values of less than 30 per cent 24 hours after starting the treatment. The reduction of the prothrombin concentration is slower and values around 30 per cent are observed only after four or five days of treatment have elapsed. The behavior of prothrombin and stable factor combined is similar to that of the prothrombin complex concentration measured by the method of Quick, with some differences which will be described in detail in a separate communication.[12]

The Combined Use of Prothrombopenic Agents

Our experience as well as that of others[13-14] shows that Tromexan has an earlier prothrombopenic effect than other similar drugs. Nevertheless prolonged treatment with Tromexan presents serious disadvantages, since the daily dose varies widely in different and even in the same patient. This accounts for a higher proportion of values beyond the therapeutic margin. Trying to eliminate this drawback while profiting from its earlier effect, Tromexan has been used in combination with other prothrombopenic agents for the initial dose.

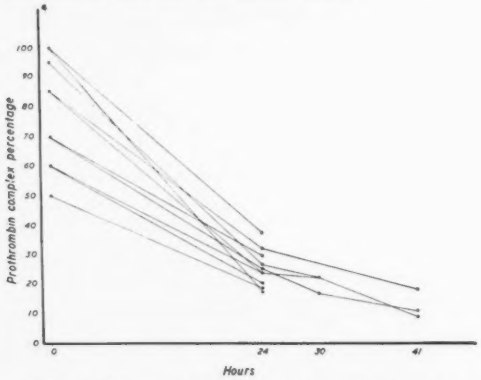


FIG. 6. Effect of a combined dose of Dipaxin (30 mg.) and Tromexan (1500 mg.) on the prothrombin complex concentration in 10 individuals.

In 10 patients 1500 mg. of Tromexan and 30 mg. of Dipaxin were simultaneously given. The prothrombin complex measured exactly 24 hours after was between 37 and 17 per cent as shown in figure 6. The maintenance treatment was followed with Dipaxin alone and the patients reacted in the same way as when receiving Dipaxin without Tromexan. In none of the 10 patients was it necessary to give the prothrombopenic agent on the second day.

In another 10 patients 1500 mg. of Tromexan and 200 mg. of Danilone were simultaneously given. The prothrombin complex measured exactly 24 hours after was between 50 and 17 per cent.

The association of Tromexan with Dipaxin produces an earlier useful prothrombin complex depression, which does not reach dangerous levels with the dosage used. After this combined initial dose, treatment is continued as if only one agent had been given.

DISCUSSION

The data presented above show that Dipaxin is a potent prothrombopenic agent. In all our cases the therapeutic level was reached between 24 and 41 hours after a 30 mg. initial dose. This contrasts with the experience of Pascale and Olwin[5] who observed this result in an average of 60 hours. This discrepancy is probably due to our larger initial dose of 30 mg. as compared with their dose of 25 mg. The average values of Pascale and Olwin[5] for the one-stage prothrombin method are slightly higher than those for the two-stage method. In our hands Dipaxin has shown a definitely earlier effect than Dicumarol, a finding contrary to that of Field and co-workers[3] which can be explained by the lower initial dose they used. The daily maintenance dose of Dipaxin fluctuates very little in the same patient and even in different individuals, being on the average 3 to 5 mg. This is the same dose used by Pascale and Olwin[5] and very similar to that of Field and colleagues.[3]

The recovery period of the prothrombin complex after withdrawal of Dipaxin is longer than that for Tromexan,[10] Danilone[1] and Dicumarol.[1] Most of our patients reach a

pretreatment level of prothrombin complex 132 hours after a single dose of Danilone and 156 hours after a single dose of Dicumarol. On the contrary, none of our cases had attained the pretreatment level 139 hours after a single dose of Dipaxin. Cyclocumarol (Cumopyran) has even a longer recovery period than Dipaxin, being of about 13 days according to our experience.[10] The apparent disadvantages of this long recovery period of Dipaxin is counteracted by the clear-cut antagonism of vitamin K_1. Small oral doses are sufficient to bring back to safe values exaggerately reduced prothrombin complex concentrations without rendering the patient refractory to the continuation of treatment. With high intravenous doses a rapid normalization of the prothrombin complex is obtained.

One of the main disadvantages of the anticoagulant treatment with prothrombopenic drugs is the long period of time necessary to obtain a therapeutic prothrombin complex level. This makes the administration of heparin necessary during the first two or three days after the embolic episode. When Dipaxin, a relatively slow acting prothrombopenic drug, is given in combination with Tromexan for the initial dose, a useful level of prothrombin complex is always obtained within 24 hours. This permits the withdrawal of heparin after the first day which is both convenient and economical. When using Dipaxin and Tromexan, the recommended doses are 30 and 1500 mg., respectively. When the treatment is started with this combination, the prothrombin complex values do not reach dangerous levels and the doses for the following days are given according to the usual schedule. The combination of prothrombopenic agents has been used by Shapiro[15] to initiate the treatment in order to eliminate the possibility of resistance to one of the drugs.

Summary and Conclusions

Dipaxin is a potent prothrombopenic agent. With an initial dose of 30 mg. the prothrombin complex reaches therapeutic levels within 41 hours. The maintenance doses vary very little in different and in the same patient (3 to 5 mg. daily).

When compared with Tromexan and Danilone the induction period of Dipaxin is longer than that of the former and shorter than that of the latter.

Vitamin K_1 readily counteracts the prothrombopenic action of Dipaxin. Small doses are effective in bringing the prothrombin complex from dangerous to safe values and large intravenous doses rapidly restore the prothrombin complex to normal.

Dipaxin acts first on the stable component and only later on the prothrombin itself.

The clinical results obtained during the anticoagulant treatment with Dipaxin are similar to those observed with other prothrombopenic drugs. The incidence of hemorrhage in our series was only 1.76 per cent. No other untoward effects were observed.

The combination of 1500 mg. of Tromexan and 30 mg. of Dipaxin for the initial dose results in a therapeutic prothrombin complex level at the twenty fourth hour. This has the great advantage of limiting the use of heparin only to the first day of treatment. After this combined initial dose, no dangerous level of prothrombin complex has been observed and the future therapeutic schedule is not changed.

Sumario Español

Se da cuenta de la experiencia con Dipaxin un nuevo y potente agente protrombopénico. Con una dosis inicial de 30 mg. se obtienen en 41 horas valores de complejo protrombínico dentro de límites terapéuticos. La dosis diaria de mantención es muy poco variable y oscila entre 3 y 5 mg.

Comparado el Dipaxin con el Dicumarol y el Tromexan demuestra tener una acción más rápida que el primero y más lenta que el segundo.

La vitamina K_1 es un antagonista eficaz de la acción protrombopénica del Dipaxin: pequeñas dosis por vía oral lleva los valores de complejo protrombínico de límites peligrosos al margen terapéutico; dosis altas por vía endovenosa neutraliza rápidamente los valores.

El efecto del Dipaxin se ejerce primeramente sobre el factor estable y sólo más tarde sobre la protrombina propiamente tal.

Los resultados obtenidos con el Dipaxin en

el tratamiento de la enfermedad tromboembólica son similares a los ya conocidos con otros agentes protrombopénicos. Como complicación en nuestra serie se presentó un 1,76 por ciento de hemorragias.

La combinación de la dosis inicial de 30 mg. de Dipaxin con 1500 mg. de Tromexan lleva a valores de complejo protrombínico bajo 30 por ciento en 24 horas, lo cual tiene la ventaja de limitar el uso de la heparina al primer día de tratamiento. Con esta dosis combinada no se han apreciado valores peligrosos de complejo protrombínico y el tratamiento puede continuarse con Dipaxin solo según el esquema habitual.

REFERENCES

[1] Katz, R., and Ducci, H.: Un nuevo anticoagulante. Fenilindandiona (Danilone). Rev. méd. Chile **80:** 104, 1952.

[2] Correll, J. T., Coleman, L. L., Long, S., and Willy, R. F.: Diphenylacetyl-1,3-indandione as a potent hypoprothrombinemic agent. Proc. Soc. Exper. Biol. Med. **80:** 139, 1952.

[3] Field, J. B., Goldfarb, M. S., Ware, A. G., and Griffith, G. C.: Effect in man of a new indandione anticoagulant. Proc. Soc. Exper. Biol. Med. **81:** 678, 1952.

[4] Duff, I. F., Dennis, E. W., Hodgson, P. E., and Coon, W. W.: Clinical experience with a new indandione derivative: a preliminary report. Univ. Michigan M. Bull. **19:** 43, 1953.

[5] Pascale, L. R., and Olwin, J. H.: Clinical experience with a new anticoagulant, Dipaxin (2-diphenylacetyl-1,3-indandione). Circulation **9:** 230, 1954.

[6] Quick, A. J.: The physiology and pathology of hemostasis. Philadelphia, Lea & Febiger, 1951. P. 125.

[7] Owren, P. A., and Aas, K.: The control of dicumarol therapy and the quantitative determination of prothrombin and proconvertin. Scandinav. J. Clin. & Lab. Invest. **3:** 201, 1951.

[8] Stefanini, M.: Activity of plasma labile factor in disease. Lancet **1:** 606, 1951.

[9] Ducci, H., Spoerer, A., and Katz, R.: Antagonismo de los agentes protrombopénicos. To be published.

[10] Alessandri H., Ducci, H., Roeschmann, W., Katz, R., Spoerer, A., and Toriello, L.: Enfermedad tromboembólica. Tratamiento anticoagulante. Rev. méd. Chile **81:** 134, 1953.

[11] Quick, A. J., and Stefanini, M.: Effect of Dicumarol on concentration of the labile factor. Proc. Soc. Exper. Biol. & Med. **72:** 232, 1949.

[12] Ducci, H., Katz, R., Roeschmann, W., and Velasco, M.: Método de Owren para el control de la terapia anticoagulante. To be published.

[13] Vander Veer, J. B., Funk Jr., E. H., Boyer, F. R., and Keller, E. A.: Clinical evaluation of ethyl biscoumacetate (Tromexan). Am. J. Med. **14:** 694, 1953.

[14] Weiner, M., Simson, G., Burns, J. J., Steele, J. M., and Brodie, B. B.: The control of prothrombin activity with Tromexan therapy. Am. J. Med. **14:** 689, 1953.

[15] Shapiro, S.: The hypoprothrombinemia-inducing activity of Link's compound #63 (Methopyranorin). Acta haematol. **6:** 129, 1951.

The Control of Dicumarol Therapy in Myocardial Infarction by a Simple Blood Prothrombin Test

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Effective anticoagulant therapy is dependent upon adequate and reliable blood prothrombin determinations. The initiation of such therapy usually requires hospitalization. The currently available blood prothrombin tests require special laboratory facilities and trained personnel. The authors of this report present the results of Dicumarol in myocardial infarction and a simple blood prothrombin test for the control of such anticoagulant therapy. The test has been employed for more than eight years. The method has proved to be simple, accurate, and practical, and has made anticoagulants possible for patients at home as well as in the hospital.

THE VALUE of Dicumarol and heparin in the prevention of thromboembolic disease and its complications seems well established.[1-6] However, the indication for anticoagulant therapy in coronary occlusion with myocardial infarction has been challenged.[7-9] The reduction in mortality because of Dicumarol is doubted; the need for anticoagulants by "good risk" patients is questioned. The hazard of bleeding or the development of subintimal hemorrhage and resultant extension of coronary occlusion have been offered as deterrants to the use of Dicumarol alone or with heparin.

Some observers have emphasized the difficulty of maintaining adequate, safe, therapeutic prothrombin levels. The difficulty of accurately performing the prothrombin test has not been overlooked. The one-stage method is too simple and the two-stage method too complicated. The Quick prothrombin time determination is found adequate by some, while others prefer a "modification" of the Quick prothrombin test. The whole-plasma and the plasma-dilution prothrombin time exponents each have their own followers. Finally, it is observed that the one-stage prothrombin time measures a complex made up chiefly of proconvertin and prothrombin.

Disagreement exists as to whether the prothrombin time should be expressed in seconds or per cent, as an index, or as the expression of a hyperbolic curve. The types of thromboplastin, the variability of thromboplastic activity, the inability to standardize a uniform thromboplastin have also presented problems which required study.

The added cost to the patient has been stressed. The requirement of trained technical personnel and adequate laboratory facilities have been considered to make the use of anticoagulants in the home difficult or even impracticable.

The psychologic factors, including the inconveniences to the patient and the psychic trauma produced by repeated venepunctures, have not been slighted.

Despite these hazards and objections, we have treated individuals with acute myocardial infarction with Dicumarol alone or with heparin, in the home and in the hospital. Since 1946, a total of 300 subjects with one or more myocardial infarcts have been studied. One hundred fifty without anticoagulants served as controls; the other 150 received Dicumarol and heparin. Both groups otherwise followed the same regimen and medication.

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TABLE 2.—*A Comparison of the Bedside Prothrombin Test with the Quick, and the Link-Shapiro Methods**

Days of treatment	Patient														
	E. G.			J. B.			M. S. M.			E. S. G.			M. M.		
	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.
1	86	88	84	92	100	86	96	88	94	90	100	96	100	100	100
2	51	35	50	84	88	80	92	42	96	85	90	96	100	100	100
3	42	20	39	51	32	60	76	50	65	83	52	84	76	53	78
4	40	20	42	42	30	43	45	34	40	68	36	72	62	34	64
5	30	24	34	40	31	42	43	32	37	55	30	58	46	23	42
6	36	16	37	34	24	33	47	26	31	41	23	46	33	18	38
7	32	10	29	36	10	31	38	10	33	40	20	32	32	10	34
8	33	12	36	32	8	30	33	8	33	42	21	41	37	10	40
9	31	10	36	39	20	30	38	12	31	41	20	38	33	12	37
10	38	28	33	39	24	38	32	5	31	32	15	28	30	8	34
11	30	22	31	38	22	37	31	5	32	33	16	29	36	10	36
12	42	31	42	30	8	30	30	5	34	32	10	28	40	10	40
13	34	12	33	42	28	30	36	10	30	36	14	34	30	8	36
14	40	30	32	34	10	36	34	5	35	36	16	34	36	8	30
15	40	32	44	40	12	36	38	10	35	36	17	32	33	5	30
16	30	5	38	40	10	31	33	5	34	30	8	22	32	10	36
17	31	8	30	30	5	35	30	5	36	31	5	26	32	10	32
18	38	26	36	38	10	35	32	5	32	36	16	34	36	12	38
19	39	26	31	31	8	37	32	5	25	31	12	24	33	8	33
20	48	32	50	39	8	31	38	10	30	39	14	36	35	10	35
21	65		66	48	29	52	35	10	30	36	15	32	37	11	39
22	68	46	65	65	54	38	40	12	36	42	20	38	31	5	30
23	56	34	53	53	44	48	48	18	48	48	22	52	30	5	30
24	66	43	60	48	32	48	40	14	40	58	24	60	36	10	40
25	48	34	42	43	23	38	46	18	38	64	34	76	36	10	36
26	38	28	32	40	10	35				72	40	80	40	18	42

Days of treatment	Patient																	
	H. L.			H. A.			M. D.			W. S.			F. L.			H. M.		
	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.
1	100	100	100	100	100	100	100	100	100	100	88	100	100	88	100	95	92	90
2	100	100	100	96	86	100	88	50	96	90	74	90	100	90	100	89	76	84
3	57	32	55	80	54	76	52	23	48	88	44	87	62	40	76	69	43	68
4	32	21	36	52	50	50	36	17	34	89	41	88	58	32	64	59	40	55
5	31	19	40	63	31	58	32	10	38	80	40	80	45	27	50	55	28	50
6	57	28	55	41	24	38	42	11	40	80	30	80	37	12	38	49	19	42
7	57	27	56	30	10	28	34	10	36	61	30	62	44	16	48	50	21	44
8	49	21	50	32	14	24	32	12	30	57	23	56	30	10	30	48	18	38
9	45	18	47	39	20	32	36	10	36	36	21	40	38	18	34	33	10	30
10	45	21	45	36	14	32	38	12	34	39	10	38	38	10	32	31	8	33
11	35	10	36	30	20	37	36	10	36	35	12	32	46	18	48	32	10	34
12	37	10	36	32	12	29	34	10	36	32	10	30	37	10	39	36	10	31
13	37	10	40	36	19	34	36	10	34	39	18	39	32	10	36	37	12	38
14	34	8	36	33	10	30	42	18	40	38	10	38	36	8	40	39	14	38
15	39	10	40	31	8	30	40	18	40	30	10	34	30	5	32	32	12	34
16	40	10	40	30	10	34	36	18	34	30	8	30	38	10	30	39	12	37
17	38	10	40	35	10	32	41	18	42	40	12	46	32	10	36	40	22	42
18	40	10	40	38	12	36	50		52	35	10	40	40	18	38	45	14	48
19	37	12	37	50	23	48	50	22	50	40	18	42	40	18	44	42	10	36
20	36	10	36	83	46	85	58	24	56	46	20	50	46	20	40	40	10	42
21	33	16	35	100	51	92	66	31	60	56	22	50	42	22	46	60	30	64
22	30	10	34	100	72	100	68	38	68	60	31	64	67	35	68	65	40	66
23	38	10	42				61	38	60	66	32	64	76	48	78	69	43	68
24	48	18	48				68	34	70	68	34	72	66	43	68	82	54	86
25	60	24	64				67	33	70	76	52	80	65	44	69			
26	64	34	68				72	37	78	80	68	84	72	50	76			

Days of treatment	Patient														
	B. S.			N. D.			H. C.			W. L.			C. A. W.		
	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.	B.	Q.	L.S.
1	72	84	66	95	83	90	100	85	96	78	80	80	88	80	90
2	48	36	48	88	52	84	90	76	87	80	52	78	90	55	87
3	38	10	42	78	40	80	85	51	82	56	31	52	78	43	95
4	38	10	36	69	38	68	83	50	80	40	20	36	69	40	66
5	32	10	32	66	38	72	82	50	78	36	10	32	66	40	64
6	36	12	42	61	30	56	68	43	67	34	10	32	61	30	58
7	34	12	38	42	21	40	55	30	54	39	12	36	42	15	40
8	32	10	34	40	18	36	51	31	53	40	18	37	40	10	40
9	32	10	32	36	15	32	42	20	41	31	10	32	36	10	34
10	33	8	36	32	10	30	40	20	38	30	10	33	32	5	30
11	31	10	32	42	15	40	32	10	31	30	5	33	42	12	40
12	32	8	38	32	12	30	33	10	39	44	15	41	32	10	33
13	34	14	30	33	10	34	30	8	32	32	12	35	38	10	39
14	30	10	36	38	12	32	36	12	34	31	10	34	34	10	31
15	34	10	32	39	18	30	30	10	38	36	10	32	39	14	37
16	35	12	38	32	10	30	36	14	34	30	18	32	33	14	31
17	34	21	32	33	8	30	31	12	39	34	16	31	30	10	37
18	36	20	30	31	10	38	36	10	33	40	18	34	41	12	46
19	32	10	32	39	10	35	30	10	37	38	18	36	40	12	37
20	34	12	32	39	12	38	30	12	36	53	20	50	46	14	34
21	44	21	44	37	10	37	36	12	32	60	30	58	40	18	42
22	64	30	60	48	23	47	40	18	38	68	32	72	58	21	57
23	70	34	74	50	22	54	48	20	49	72	40	78	62	30	68
24	76	36	78	64	30	68	56	21	58	76	43	80	66	36	71
25	82	40	82	68	33	62	60	30	67	80	50	76	73	50	84
26	86	53	80	65	38	61	68	37	72	84	52	88	85	60	88

B., Bedside test; Q., Quick test; L.S., Link-Shapiro test.

* Prothrombin time expressed in per cent.

Moreover, owing to inadequate laboratory facilities, lack of laboratory technicians and our awareness of the inaccuracy, variability, multiplicity and preferability of prothrombin methods, we employed a simple capillary blood prothrombin test, a modification of the Ziffren-Smith whole blood prothrombin test.[10] The test was modified to a micromethod for bedside use; a procedure so simple that it can be performed by a completely inexperienced but conscientious, interested person. Two to three minutes are required to obtain a prothrombin time.

The purpose of this report is to describe a simple blood prothrombin test and to present the results of Dicumarol therapy regulated by this method.

Materials and Methods

The 300 patients studied were under direct supervision of the authors either at home or in the hospital. Alternate cases in the first 224 patients received conventional therapy and constitute the "control" group, while the others received Dicumarol, alone or with heparin, in addition to conventional therapy and represent the anticoagulant group. The remaining 76 patients were selected according to the day first observed. Those first examined on the odd calendar date received anticoagulants while those seen on the even calendar date were placed in the control group. In addition to the clinical and laboratory findings, electrocardiographic confirmation of myocardial infarction was required for inclusion in the study.

Most of the patients were seen within 72 hours of the onset of their illness. Seventy-five subjects were seen one week after the onset of the acute coronary occlusion; 37 were in the control and 38 were in the anticoagulant group. All patients who died within the first 24 hours were not included in the present report.

A comparison of the patients in the two groups with regard to age, sex, previous infarction and severity of the present attack according to "good" and "poor" risk[11] are shown in table 1. The ages ranged from 31 to 81 years with a mean age of 58.5 for the anticoagulant and 61 for the control group. Forty-two and 48 per cent were 61 years old or over in the anticoagulant and control groups, respectively. Sixteen per cent in the treated group and 19.4 per cent in the control group were females.

A history of one or more previous myocardial infarctions was noted in 28 per cent in the anticoagulant group and in 23 per cent of the control group.

In the anticoagulant group 72 per cent received heparin and Dicumarol and 28 per cent received Dicumarol alone. The initial dose of Dicumarol was 200 to 300 mg. and thereafter 100 mg. daily until the prothrombin level was in the therapeutic range. For those who received heparin the prothrombin test was made three to four hours after the last dose or when the clotting time was normal. Daily prothrombin determinations were performed during the first 30 days, then repeated at weekly intervals for six or more weeks.

Technic

The bedside method is a modified Ziffren-Smith prothrombin test. Two hemoglobin pipets, a concave slide, stop watch, physiologic saline solution and thromboplastin are the required materials. (See fig. 1.) The thromboplastin is prepared from acetone-desiccated rabbit brain as recommended by Quick.[12] To 4 cc. of physiologic saline solution

Table 1.—*Composition of Total Group: 300 Cases of Coronary Occlusion with Myocardial Infarction Surviving First Day of Illness*

	Anticoagulant	Control
No. of Cases	150	150
Av. Age	58.5	61
Males	126 (84%)	121 (80.6%)
With Previous Infarct	42 (28%)	34 (23%)
Good Risks	33 (22%)	47 (31%)
Poor Risks	117 (78%)	103 (69%)
Heparin and Dicumarol	108 (72%)	0
Dicumarol Alone	42 (28%)	0
Thromboembolic Complications	9 (6%)	26 (17.3%)
Mortality	18 (12%)	42 (28%)

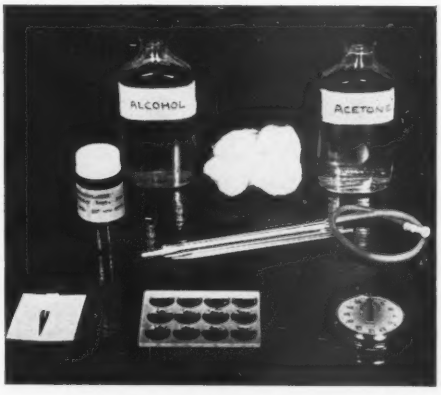

Fig. 1

0.15 Gm. of dried powdered rabbit brain is added. The mixture is then incubated for 20 minutes at 40 C.

Twenty cu. mm. of thromboplastin warmed to 37 C. are placed on a warm dry slide, and an equal amount of free-flowing capillary blood, obtained by a simple needle puncture of a finger, is added. The slide is tilted gently back and forth until a coagulum is formed. The time in seconds is the prothrombin time. The "total clotting time" for capillary blood is 15 to 18 seconds, with a standard deviation of 2.5 seconds. A normal blood prothrombin time on a control is always taken before it is determined on a patient. The therapeutic level is maintained at twice the normal (36 to 40 seconds). When the prothrombin time is expressed as a percentage of the normal the therapeutic level was maintained between 40 and 60 per cent. The equation for this determination is

$$\textit{Prothrombin index} = \frac{\textit{normal prothrombin time}}{\textit{patient's prothrombin time}} \times 100$$

A comparison of this method with the Quick and Link-Shapiro blood prothrombin tests is shown in table 2. It compares favorably with the Link-Shapiro method. The values expressed in per cent in the Quick blood prothrombin test are based on a hyperbolic dilution curve. When the bedside prothrombin test, expressed in per cent, is 60 to 40, this corresponds to Quick prothrombin time expressed as 30 to 10 per cent, respectively. The bedside prothrombin test is discussed in greater detail in another report to be published.[13]

Results

The subjects in both groups were classified with regard to prognosis according to the criteria of Russek and his co-workers[11] as "good risk" and "poor risk" patients. Those who had previous myocardial infarction, angina pectoris, intractable pain, severe shock, cardiomegaly, congestive heart failure, auricular fibrillation or other serious arrhythmia, previous pulmonary embolism, or other states predisposing to thrombosis, were placed in the "poor risk" category. Patients without the above signs or symptoms were classified as "good risks." The grouping was made on the clinical examination excluding the electrocardiographic and other laboratory data.

The total mortality in the control group was 42, or 28 per cent, and in the anticoagulant group, 18 or 12 per cent (table 1). Clinical thromboembolic phenomena occurred in 26, or 17.3 per cent and in nine, or 6 per cent, in the control and anticoagulant groups, respectively.

Among the 47 good-risks in the control group, the mortality was six, or 12.8 per cent. Among the 33 good risks in the anticoagulant group there were three deaths, or 9.1 per cent.

Thromboembolism occurred in two of the good risks, or 4.2 per cent. Embolism was fatal in both of these cases. Death occurred 14 and 18 days, respectively, after the onset of illness and during otherwise uneventful convalescence. In the anticoagulant group thromboembolism also occurred in two patients, but the patients recovered from this complication.

The mortality in the 103 poor risks in the control group was 36, or 35 per cent, whereas in the anticoagulant group of 117 there were 15 deaths of 12.8 per cent. Thromboembolic complications in these poor risks showed a corresponding contrast. They occurred in 24, or 23.3 per cent, of the control group and in only seven, or 5.9 per cent, of the anticoagulant group. Death due to pulmonary embolism occurred 12 times among poor risks in the control group and once in the anticoagulant group. Pulmonary embolism in the remaining cases of both groups complicated by thromboembolism was the precipitating cause of severe congestive heart failure.

In poor risks with two or more myocardial

Table 3.—*Mortality Rate and Incidence of Thromboembolic Complications in Control and Anticoagulant Groups*

	No. of Cases		Mortality		Embolism	
	Control	Anticoag.	Control	Anticoag.	Control	Anticoag.
Good Risk	47	33	6 (12.8%)	3 (9.1%)	2 (4.2%)*	2 (6.0%)†
Poor Risk	103	117	36 (35%)	15 (12.8%)	24 (23.5%)	7 (5.9%)
Total	150	150	42 (28%)	15 (12%)	26 (17.3%)	9 (6.0%)

* Fatal. † Recovered.

TABLE 4.—*Mortality Rate and Incidence of Thromboembolic Complications in Patients with Previous Infarction*

	No. of Cases	Mortality		Embolism	
		No.	%	No.	%
Anticoag.	42	9	21.3	4	9.3
Control	36	21	58.3	14	38.8

infarctions treated with Dicumarol the prognosis was better than in the comparable control patients. Among 42 such patients who received anticoagulant therapy, nine died, or 21.3 per cent (table 4). Embolization occurred four times, or in 9.9 per cent. In the control group of 36 subjects there were 21 fatalities, or 58.3 per cent, and embolism occurred in 14 subjects, or 38.8 per cent.

The causes of death in the control group of 150 were as follows: In 12 patients death followed pulmonary embolism; two patients died of ruptured hearts 14 and 20 days, respectively, after onset of the illness; 20 died of congestive heart failure; four died of extension of the myocardial infarct; and in four the cause of death was undetermined. Of 15 fatalities in the entire anticoagulant series of 150, one was due to pulmonary embolism, nine to congestive heart failure, three to sudden unexplained death, one to respiratory depression following intravenous morphine, and four to unknown causes.

Hemorrhagic complications were noted in 16, or 10.6 per cent of treated patients. The hemorrhagic manifestations were distributed as follows: epistaxis in two, ecchymoses on the body in eight, hematuria in four, and hematemesis and hemoptysis in two. If one excludes epistaxis and ecchymoses, the incidence of hemorrhagic complications would be six, or 4 per cent. There were no deaths from hemorrhage in the group treated with anticoagulants. Hemorrhagic complications were the cause of death in two, or 1.33 per cent of the control group, as a result of ventricular rupture and cardiac tamponade.

DISCUSSION

The greatest deterrent to the use of Dicumarol therapy is the fact that a simple, accurate and inexpensive method for measuring blood prothrombin activity has not been available. Methods currently employed require trained technical personnel and laboratory facilities. The present report is unique in one respect; Dicumarol has been given to patients with coronary thrombosis and infarction in the home as well as in the hospital. Effective antithrombotic levels as measured by a simple blood prothrombin test were maintained without the increased hazard of bleeding.

Whole blood for performing a blood prothrombin test has been employed by many investigators in the past. A similar method employing capillary blood was first described by Quick in 1939.[14] Tocantins[15] has employed whole venous blood for the Ziffren-Smith prothrombin test in his routine control of anticoagulant therapy. Bruzelius[16] in Sweden has used a similar micromethod for Dicumarol therapy. Several modifications of a similar type of prothrombin test have been reported.[17-21] So far as is known, the present report is the first to deal with a large series of patients with acute myocardial infarction in which Dicumarol dosage has been controlled by such a simple blood prothrombin test.

A comparison of this bedside prothrombin test with current one-stage procedures shows it to have much in common with the latter. The term "prothrombin test" for such methods is a misnomer. Both measure more than prothrombin activity. It has been shown that the one-stage prothrombin test measures prothrombin, fibrinogen, and accelerator factors.[22] The prothrombin time, therefore, is an accelerated "clotting test" and reflects more than prothrombin concentration.

The present method is not without its pitfalls. The accuracy and sensitivity of this test was dependent upon an active and reliable source of thromboplastin. While normal plasma yielded the same prothrombin time with different types of thromboplastin, Dicumarol plasma behaved differently with various types of thromboplastin. The results reported here can only be reproduced if desiccated acetone-dehydrated rabbit brain is used as the source of thromboplastin. The thromboplastin activity may vary with the age, temperature and

amount employed. A control prothrombin time must always be determined first on a normal subject.

The described test has proved a valuable practical guide to Dicumarol therapy for the prevention of thromboembolic complications. At the same time it was possible to detect hypoprothrombinemia and to prevent hemorrhagic complications. The usefulness of the simple blood prothrombin test which we have employed for the control of Dicumarol therapy is reflected in the therapeutic efficacy and safety noted in this series. The results compare favorably with the reports of other investigators using other prothrombin tests.

Those who challenge the value of anticoagulant therapy have suggested that the favorable results noted in the literature may be due primarily to the added attention given to all patients who have received anticoagulant drugs. Every effort was made in the study to follow an identical medical regimen and provide the same attention to the patients in both groups.

It has been postulated that in addition to prevention of thromboembolic complication, anticoagulants prevent congestive failure, ventricular fibrillation and cardiac asystole by the prevention of intravascular coronary thrombosis. Gilbert and Nalefski[23] have suggested that the favorable results observed from Dicumarol were due primarily to an increase in coronary blood flow. Gilchrist[24] believed that in addition to the reduction in thromboembolism, anticoagulants had a favorable influence on the associated shock syndrome.

The collective statistics from the proponents of anticoagulant therapy have been critically probed for defects and inaccuracies. Those who challenge the value of anticoagulant therapy emphasize the comparable low incidence of mortality in good risks not treated with anticoagulants. The occasional thromboembolic complication would have little influence on the over-all mortality rate and hence would justify their view. However rare, this complication did occur and proved fatal to two in our control group. While the increased mortality from such a complication was only 4.2 per cent, hardly significant statistically, the unpredictability of such a complication in a good risk increased the responsibility of avoiding a preventable fatality from thromboembolism. To a family, the survival of such a patient assumes greater importance than any significant statistical figure. These observations are in agreement with Wright's[25] earlier admonitions.

One critic has agreed that anticoagulants are indicated in the poor risk. The mortality in the control group was 35 per cent as against 12.3 per cent in the anticoagulant group. Death was nearly three times more frequent in the control group. Thromboembolic complications showed a decrease in the anticoagulant group. The prognosis in the poor risk group with two or more myocardial infarctions treated with Dicumarol was better than in the comparable control group. The mortality was reduced from 58.3 per cent to 21.3 per cent, and embolization from 38.8 to 9.3 per cent. These results have afforded an increased sense of security and a more favorable prognosis. It was not vitiated by either anxiety or fear of hemorrhage. The results of this study indicate that the advantages of Dicumarol therapy were greater than all the disadvantages reported to date.

The hazard of hemorrhage was nevertheless present. Without careful clinical observation, attention to detail, and an awareness of idiosyncracies, many medicaments are dangerous and even fatal. The incidence of hemorrhagic complications was low and compares well with previous reports. Frequent prothrombin determinations made it possible to detect levels of hypoprothrombinemia before hemorrhagic complications developed. The withdrawal of Dicumarol and administration of vitamin K, orally or parenterally, was always effective in stopping these manifestations. It was unnecessary to hospitalize the patient or to administer blood. Bleeding usually ceased within 6 to 10 days. There were no deaths from this cause.

Summary

The control of Dicumarol therapy in acute myocardial infarction by a simple capillary blood prothrombin test has proved convenient,

practical and economical. It was possible to administer anticoagulant therapy to 150 patients with myocardial infarction at home and in the hospital. An additional 150 subjects who did not receive anticoagulants served as controls. Except for Dicumarol, alone or with heparin, both groups followed the same regimen and received the same medication.

Mortality in the anticoagulant group was 12 per cent; in the control group it was 28 per cent. Among 33 subjects in the "good risk" group treated with Dicumarol, there were three deaths (9.1 per cent); while in 47 of the good risks in the control group, the mortality rate was six (12.8 per cent). The mortality among 117 cases of the "poor risk" anticoagulant group was 15 (12.8 per cent). Among the poor risks of the control group of 103 cases, there were 36 deaths (35 per cent).

Thromboembolic complications developed in nine (6 per cent) of the treated patients as against 26 (17.3 per cent) in the control group.

Death due to pulmonary embolism occurred in one subject (0.66 per cent) in the treated group and in 12 (8 per cent) in the control group. Two of the deaths in the latter group occurred among the good risks. The prognosis in the poor risk group with two or more myocardial infarctions treated with Dicumarol was better than among poor risks of the control group.

Hemorrhagic complications were noted in 16 (10.6 per cent) of the treated and in two (1.33 per cent) of the control group.

The advantages of Dicumarol therapy, properly administered, were greater than all the disadvantages reported to date.

The value of the simple blood prothrombin test employed for the control of Dicumarol therapy is reflected in the therapeutic efficacy and safety noted in this series. It compares favorably with the reports of other investigators using other prothrombin tests.

Sumario Español

El control de la terapia de Dicumarol en el infarto del miocardio agudo por medio de una prueba sencilla de protrombina capilar sanguínea ha probado ser conveniente, práctico y económico. Fué posible administrar terapia anticoagulante a 150 pacientes con infartos del miocardio en su hogar y en el hospital. Unos 150 casos adicionales que no recibieron anticoagulantes sirvieron de controles. Excepto por Dicumarol, solo o con heparina, ambos grupos siguieron el mismo régimen y recibieron el mismo medicamento.

La mortalidad en el grupo a que se les administró anticoagulante fué de 12 por ciento; en el grupo control fué 28 por ciento. Entre 33 sujetos en el grupo "buen riesgo" tratados con Dicumarol, ocurrieron tres muertes (9.1 por ciento); mientras que en 47 de los buenos riesgos en el grupo control, la mortalidad fue de seis (12.8 por ciento). La mortalidad entre 117 casos de los riesgos pobres en el grupo tratado con anticoagulante fué 15 (12.8 por ciento). Entre los riesgos pobres en el grupo control de 103 casos, hibieron 36 muertes (35 por ciento). Complicaciones tromboembólicas se desarrollaron en nueve (6 por ciento) de los pacientes tratados en contraste a 26 (17.3 por ciento) del grupo control.

Muerte debida a embolismo pulmonar ocurrió en un sujeto (0.66 por ciento) en el grupo con anticoagulante y en 12 (8 por ciento) del grupo control. Dos de las muertes en este último grupo ocurrieron entre los buenos riesgos. El prognóstico en el grupo de riesgo pobre con dos o más infartos del miocardio tratados con Dicumarol fué mejor que en el grupo de pobres riesgos en el grupo control.

Complicaciones hemorrágicas fueron observadas en 16 (10.6 por ciento) de los tratados y en dos (1.33 por ciento) del grupo control. Las ventajas de la terapia con Dicumarol propiamente administrada, fueron mayores que todas las desventajas informadas hasta la fecha.

El valor de la prueba sencilla de protrombina sanguínea empleada en el control de la terapia con Dicumarol se refleja en la eficacia terapéutica y la inocuidad notada en esta serie. Compara favorablemente con los informes de otros investigadores usando otras pruebas de protrombina.

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REFERENCES

[1] Nichol, E. S., and Page, S. W., Jr.: Dicumarol therapy in acute coronary thrombosis. Results in 50 attacks. J. Florida M.A. **32:** 365, 1946.

[2] Parker, R. I., and Barker, N. W.: The use of anticoagulants in the management of acute myocardial infarction. Proc. Staff Meet., Mayo Clin. **22:** 185, 1947.

[3] Peters, H. R., Doriges, J. P., and Brambel, C. E.: Further experiences with dicumarol therapy in coronary thrombosis. South. M. J. **41:** 526, 1948.

[4] Wright, I. S., Marple, C. D., and Beck, D. F.: Anticoagulants in treatment of coronary thrombosis with myocardial infarction. Am. Heart J. **36:** 801, 1948.

[5] Greisman, H., and Marcus, R. M.: Acute myocardial infarction: detailed study of dicumarol therapy in 75 consecutive cases. Am. Heart J. **36:** 600, 1948.

[6] Smith, F. J., Keyes, J. W., and Denham, R. M.: Myocardial infarction. Am. J. M. Sc. **221:** 508, 1951.

[7] Russek, H. I., Zohman, B. L., White, L. G., and Doerner, A. A.: Indications for dicumarol in acute myocardial infarction. J.A.M.A. **145:** 390, 1951.

[8] Littman, D.: The prevention of thrombo-embolism in acute myocardial infarction. New England J. Med. **247:** 205, 1952.

[9] Baer, S., Krasnoff, S. O., and Heine, W.: Criteria for the use of anticoagulants in acute myocardial infarction. Pennsylvania M. J. **56:** 274, 1953.

[10] Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P.: A simple bedside test for control of vitamin K therapy. Am. J. Clin. Path. **10:** 13, 1940.

[11] Russek, H. I., and Zohman, B. L.: Present status of anticoagulant therapy in acute myocardial infarction. Quart. Rev. Med. **9:** 1, 1952.

[12] Quick, A. J.: The hemorrhagic diseases. Springfield, Ill., Charles C Thomas, 1942.

[13] Manchester, B.: A simple blood prothrombin test for the control of dicumarol therapy. M. Ann., District of Columbia (To be published).

[14] Quick, A. J.: Determination of prothrombin. Proc. Soc. Exper. Biol. & Med., **42:** 788, 1939.

[15] Tocantins, L. M.: Personal communication. 1949.

[16] Bruzelius, S.: Dicoumarin in clinical use; studies on its prophylactic and therapeutic value in treatment of thrombo-embolism. Acta chir. scandinav. **92:** 1, 1945.

[17] Kato, K.: Micro-prothrombin test with capillary whole blood. Am. J. Clin. Path. **10:** 147, 1940.

[18] Abramson, D. J., and Weinstein, J. J.: A rapid bedside micro-prothrombin test. Am. J. Clin. Path. **12:** 1, 1942.

[19] Innes, J., and Davidson, L. S. P.: A simple method of estimating prothrombin in capillary blood. Brit. M. J. **1:** 621, 1941.

[20] Brafield, A. J. E., and Walther, W. W.: The control of anticoagulant therapy. Lancet **2:** 240, 1951.

[21] Bedford, P. D.: Control of anticoagulant therapy. Lancet **2:** 640, 1951.

[22] Alexander, B., deVries, A. and Goldstein, R.: Prothrombin: a critique of methods for its determination and their clinical significance. New England J. Med. **240:** 403, 1949.

[23] Gilbert, N. C., and Nalafski, L. A.: The effect of heparin and dicumarol in increasing the coronary flow volume. J. Lab. & Clin. Med. **34:** 797, 1949.

[24] Gilchrist, A. R.: Coronary thrombosis and its response to treatment. Brit. M. J. **2:** 351, 1952.

[25] Wright, I. S.: Experiences with dicumarol (3,3′ methylene-bis (4-hydroxycoumarin)) in the treatment of coronary thrombosis with myocardial infarction. Am. Heart J. **32:** 20, 1946.

Pattern of Hereditary Susceptibility in Rheumatic Fever

By MAY G. WILSON, M.D., AND MORTON SCHWEITZER, PH.D.

This study is concerned with the pattern of inheritance of susceptibility to rheumatic fever. To investigate the genetic mechanism of inheritance in rheumatic fever the families of a selected parent were brought under observation without regard for the presence or absence of rheumatic fever in the unselected mate or collateral relatives. These data are preferable for genetic analysis since they are not biased by selection of affected children and can therefore be analysed directly by the application of simple Mendelian ratios. Two hundred ninety-one families including 646 siblings were under continuous medical supervision at The New York Hospital for an average period of 10 years. Rheumatic fever occurred in 40 children among a total of 121 offspring in 52 genetically susceptible families. By contrast in 239 nonsusceptible families with a total of 525 children, there were only three children who developed rheumatic fever. Genetic analysis of the data gave good agreement with simple recessive inheritance while excluding other mechanisms. The previous conclusion that susceptibility to rheumatic fever is inherited as a simple recessive trait was corroborated.

GENETIC and epidemiologic studies in 1937[1] and 1943[2] revealed that the distribution of cases among 471 children in 113 rheumatic families was consistent with a genetic mechanism of simple recessive inheritance. These families were selected because of the presence of at least one rheumatic child. It was concluded that hereditary susceptibility is the primary factor responsible for the concentration of rheumatic fever in certain families.

An hereditary factor in rheumatic fever has been reported by other investigators. In 1952 Gray, Quinn and Quinn[3] reported agreement with a simple recessive gene hypothesis in 40 New Haven families similarly selected. There was a paucity of cases in three positive by positive matings. In a Toronto study by Uchida in 1953,[4] it was concluded from a genetic analysis of 58 affected families that no definite mode of inheritance could be established from the limited data. In 1953 Stevenson and Cheeseman[5] studied 462 families in Belfast which were ascertained by an affected child and 51 families ascertained by an affected mother. It was concluded that inheritance played a major role in determining familial aggregation of cases but that a Mendelian mechanism could not be established.

To investigate further the pattern of inheritance in rheumatic fever, the families of a selected parent were brought under observation without regard for the presence or absence of rheumatic fever in the unselected mate or in collateral relatives. These families are preferable for genetic analysis because they can be analyzed directly by the application of simple Mendelian ratios in contrast to families selected by an affected child. The latter require statistical treatment. This report is concerned with the genetic analysis of data for 646 children from 291 families who were under continuous medical supervision for an average period of 10 years.

MATERIAL

The parents selected included 224 members of the Pediatric Cardiac Follow-Up Clinic of The New York Hospital, consisting of 192 rheumatic and 32 congenital cardiac patients, 24 consecutive patients with rheumatic heart disease admitted to the Lying-In Hospital, and 43 brothers or sisters of rheumatic members of the Cardiac Clinic. The 291 families, including 646 children, were representative of a mixed population in greater New York City. The living conditions and economic status of two-thirds of the families were considered favorable.

History of the presence or absence of rheumatic fever among unselected mates and their collateral relatives was obtained on initial contact and periodically reviewed during the period of observation. The

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unselected mate and the majority of collateral relatives were given a complete physical examination at the clinic, including fluoroscopic examination of the heart. The progeny were under continuous close medical supervision in a special pediatric clinic. Periodic physical, fluoroscopic and electrocardiographic examinations were made. In addition, clinical, immunologic and biochemical investigations were conducted among these families during the period of observation.[6, 7] Routine clinic visits were made at least four times a year. Home and clinic visits were made during any intercurrent illness. The majority of children were observed from infancy. The diagnosis of rheumatic fever in parents, collateral relatives and children was based on the occurrence of manifestations of rheumatic fever confirmed by evidence of rheumatic heart disease on physical, fluoroscopic and electrocardiographic examination.[8, 9]

Method of Genetic Analysis

The data were arranged in parental mating types and appropriate Mendelian ratios applied. Standard tests for dominant, sex-linked, and recessive inheritance were made.[10]

The principal criteria for establishing Mendelian inheritance are as follows:

A. Dominant inheritance passes by direct descent from a parent to half of his children. Individuals who are negative do not transmit the condition to their offspring.

B. Sex-linked inheritance passes usually from a male to his grandson through a daughter who is unaffected. Mates who are negative do not transmit the condition. Daughters of affected males are all carriers although themselves usually unaffected, and transmit to half of their sons.

C. Recessive inheritance, unlike the other types, is transmitted through both parents. A negative individual who has no close relatives with the condition will not transmit it, and all of his children will be free from the condition regardless of the genetic circumstances of his mate. The children of two affected individuals are all expected to be affected. When an affected individual marries a carrier, one-half of the progeny are affected. Among the children of two carriers, one-fourth will be affected.

In order to compute the ratios, the carriers must first be identified. Children of affected individuals are carriers. Among the siblings of cases, two-thirds will be carriers. When the kinship of an individual is less close, the risk of being a carrier is reduced. Due to the small size of human families, carriers can not always be identified by knowledge of the kinship. When this occurs, statistical estimates are used.

D. More complex patterns of inheritance are known in animals, and to some extent in man, but the results of these will approximate the preceding, differing only in the numerical quantities. For present purposes they need not be considered.

E. In studying diseases which exhibit a range in age of onset, adjustments are necessary for children who have not reached the susceptible age. The method for making this adjustment in rheumatic fever has been previously presented.[2]

Observations

In table 1 are summarized the source and classification of selected and unselected parents. It will be noted that 222 selected parents were rheumatic, 37 were brothers and sisters of rheumatic patients and 32 were negative. Twelve of the unselected parents were rheumatic, 41 had rheumatic collateral relatives and 237 were negative.

The age distribution of children of different parental types at last observation is presented in table 2. Among 121 offspring from 52 genetically susceptible families, 89 per cent had passed the peak age of onset of rheumatic fever; 11 per cent were under 6 years of age, 44 per cent were between 6 and 13 years of age, and 45 per cent were past 13 years of age. Among the 525 children of 239 nonsusceptible families, 80 per cent had passed the peak age of onset; 20 per cent were under 6, 56 per cent were between 6 and 13 years of age, and 24 per cent had passed 13 years of age.

The ages at onset of the 43 children who developed rheumatic fever was 2 to 5 years in 25 patients, and 6 to 10 in 18 patients. All experienced one or more episodes of active carditis associated with constitutional symptoms.

Table 1.—*Source and Classification of Families by Parental Diagnosis*

	Selected Parent*			Unselected Mate		
	+	C	−	+	C	−
I	216	0	0	8	30	178
II	6	37	0	3	11	29
III	0	0	32	1	0	31
	222	37	32	12	41	238

* (I) Rheumatic parent from Cardiac Clinic or Lying-In Hospital. (II) Brothers or sisters of (I). (III) Patients with congenital heart disease from Cardiac Clinic.

In this and succeeding tables: + = rheumatic; C = nonrheumatic member of a rheumatic family (carrier); − = nonrheumatic, no rheumatic collateral relatives.

TABLE 2.—*Age Distribution of Siblings in Genetically Susceptible and Nonsusceptible Families*

Group	No. of Families	No. of Siblings			
		Total	Under 6 yrs.	6–13 yrs.	Over 13 yrs.
Genetically susceptible					
+ × +	8	15	2	8	5
+ × C	35	83	8	33	42
C × C	9	23	4	12	7
	52	121	14	53	54
Nonsusceptible					
− × −	26	61	12	39	10
+ × −	183	399	80	217	102
C × −	30	65	13	38	14
	239	525	105	294	126
	291	646	119	347	180

In 20 patients, carditis was subacute, and in two it was the only manifestation. Subcutaneous nodules occurred in four patients, 10 patients experienced one or more attacks of chorea, 25 had polyarthritis and 32 arthralgia. Epistaxis and erythema multiforme occurred in 18 patients. At last observation residual cardiac involvement was present in all of the patients. Enlargement of the left ventricle and left auricle was moderate in 34, and marked in 9 patients. Mitral insufficiency was present in 40, mitral stenosis in 3. No auscultatory murmurs were heard in three patients. There were two deaths, one due to bacterial endocarditis and one to cardiac failure.

GENETIC ANALYSIS

Genetic analysis supported the simple recessive hypothesis and excluded sex-linkage, dominant and multiple-gene hypotheses. In table 3 is presented a comparison of the number of cases so far observed and the number expected for different parental family types. The number expected at the present age was obtained by application of an age correction factor.[2] There were 52 families which were considered genetically susceptible and in this group (table 3, a–e) there were 40 cases observed among 121 siblings. The familial incidence was negligible in the genetically nonsusceptible families (lines f–h). Only three cases were observed among 525 children in 239 families.

It will be noted that of 49 cases finally ex-

TABLE 3.—*Comparison of the Number of Rheumatics Observed and Expected Based on Test for Recessive Inheritance.*

Mating Type	Families	Siblings	No. of Children Under 6 Years	Cases Observed	Cases Expected
(a) + × +	8	15	2	14	15
(b) + × C	7	20	0	10	10
(c) + × C*	28	63	8	11	21
(d) C × C	2	4	0	1	1
(e) C* × C*	7	19	4	4	2
	52	121	14	40	49
(f) + × −	183	399	80	2	0
(g) C × −	30	65	13	0	0
(h) − × −	26	61	12	1	0
	239	525	105	3	0
	291	646	119	43	49

(a) Positive mated with positive; in this mating all children are expected to be positive.

(b) Positive mated with negative who is the child of a rheumatic; half of the children are expected to be rheumatic.

(c) Positive mated with negative who is the sibling of a rheumatic; one-third of the children are expected to be rheumatic.

(d) Two negative individuals who are both children of rheumatics; one-quarter of the children are expected to be rheumatic.

(e) Two negative individuals, both of whom have some close kin who are rheumatic; fewer than one-quarter of the children are expected to be rheumatic.

(f) Positive mated with negative who has no rheumatic parentage or close kin (siblings, aunts, uncles, nieces and nephews); no rheumatic children are expected.

(g) Negative who has a rheumatic parent or sibling mated with a negative with no rheumatic parentage or close kin; no rheumatic children are expected.

(h) Both parents negative, with no rheumatic parentage or close kin; no rheumatic children are expected.

C*—nonrheumatic parent who had a rheumatic close relative other than parent. C is a nonrheumatic parent who had one rheumatic parent.

pected, 40 have so far been observed. Since all of the siblings had not passed the peak age of onset of the disease, the data were corrected for present age. On this basis, 45 cases are expected at the attained age and 43 are observed. Good agreement is noted at the attained age of the children. A few additional cases are expected in the susceptible families as the younger children reach the ages of maximum incidence. It is unlikely that any considerable number of new cases will occur at older ages. In the previously reported study,[2] 130 individuals who were nonrheumatic at the ages of 13 to 25 years have remained nonrheumatic during 11 additional years.

Comment

Genetic analysis of human data is limited by the relatively small family size as compared with experimental material. This may preclude complete expression of an hereditary trait. In addition, diagnostic difficulties may prevent adequate ascertainment of cases. This is particularly true in the diagnosis of rheumatic fever in adults since physical signs of rheumatic heart disease often regress and childhood illness is not accurately recalled. In the absence of a specific diagnostic test, complete reliance is frequently placed on historical information or a limited physical examination. In this study, evidence of rheumatic heart disease determined by physical, fluoroscopic and electrocardiographic examinations was required for confirmation of a diagnosis of rheumatic fever. In spite of the rigid diagnostic criteria utilized, there were probably a few errors in parental classification in families where information was limited concerning collateral relatives. The continuous medical supervision of the families, the majority from infancy to past the peak age of onset, minimized possible diagnostic errors in the children.

The conclusion that the pattern of inherited susceptibility is a recessive character rests on the agreement between observation and expectation. Equally important for the interpretation of recessiveness are the observations in the lower half of table 3, (f–h). The insignificant number of cases in 239 families where one parent is nonrheumatic and not known to have close kin who are rheumatic is strong evidence that recessive inheritance is involved.

Complete agreement, with a specific hereditary mechanism may not always be obtained even in conditions of proven heredity. It is well known in experimental material that certain modifying factors, endogenous or exogenous, may influence the expression of hereditary traits. This may also occur in human disease. The differences in type and severity of manifestations of rheumatic fever among members of a family suggest different degrees of susceptibility which perhaps reflect endogenous modifying influences. There are probably also exogenous factors which may influence the expression of the disease in a susceptible child.

The adequacy of recessive inheritance to describe the distribution of cases among these families does not exclude a more complicated mechanism. It is, however, the simplest hypothesis, requiring no additional assumptions.

The results of this investigation confirm the conclusion of simple recessive inheritance previously reported. It may be noted that the analytic procedures in the two studies were different. The procedures in the present study are more satisfactory because they do not require the statistical adjustments that must be made when the affected child is the index case. When data are collected based only on parental selection, the standard Mendelian methods of analysis are fully adequate. Where information on the antecedents of the parents is meager, statistical analysis based on estimates of population frequency is used to determine the pattern of inheritance. This method of analysis requires a series of families collected as a random sample. This important condition is not fulfilled in clinic families, and the use of this method is therefore not warranted.

The primary role of heredity in the familial concentration of rheumatic fever has been confirmed in this and other published investigations. These observations emphasize the importance of identifying the genetically susceptible family to facilitate early diagnosis and treatment. The medical supervision of these families affords an opportunity for investigation of the nature of the inherent factor responsible for susceptibility. They are also useful for

the study of exogenous factors which may be responsible for the development of rheumatic fever in a susceptible child. Current etiologic concepts may be explored within this framework. Clinical, immunologic and biochemical pilot investigations have so far revealed no significant differences among susceptible and nonsusceptible children in these families. It is of interest that the incidence and frequency of illness, particularly respiratory infections, was comparable in the two groups.

The demonstration of hereditary susceptibility does not exclude the operation of environmental factors. Like most published family studies the present investigation concerns a clinic population which excludes families of higher economic level. The economic status and living conditions which prevailed among the susceptible and nonsusceptible families was comparable and far superior to those in the earlier investigation.

It is frequently stated that the incidence of rheumatic fever may be declining. The data collected during the past 25 years have been examined in order to see whether the familial incidence has changed. There is no evidence of reduced penetrance in recent years. This is apparent in the positive by positive families where the observed incidence in families completed 10 or more years ago is the same as in the current series. It is of interest that the age of onset and pattern of rheumatic fever were comparable in both series of families. These observations would seem to indicate that the prevalence and pattern of rheumatic fever in greater New York City has not changed significantly in the past two decades.

Summary

The families of 291 selected parents including 646 children were under continuous medical supervision for an average period of 10 years.

The parents selected included 224 members of the Pediatric Cardiac Follow-Up Clinic of The New York Hospital, 24 consecutive patients with rheumatic heart disease admitted to the Lying-In Hospital, and 43 brothers or sisters of rheumatic members of the Cardiac Clinic.

Forty of 121 children from genetically susceptible families developed rheumatic fever compared with 3 of 525 children from nonsusceptible families.

Genetic analysis of the various mating types gave good agreement with simple recessive inheritance while excluding other mechanisms. Corroboration of the previous conclusion that rheumatic fever susceptibility is inherited as a simple recessive trait was obtained.

Sumario Español

Las familias de 291 padres seleccionados incluyendo 646 hijos estuvieron bajo continua supervisión médica por un tiempo promedio de 10 años.

Los padres seleccionados incluyeron 224 miembros de la Clínica Cardíaca de Progreso "Follow-up" de Pediatría del Hospital de Nueva York, 24 pacientes consecutivos con enfermedad reumática del corazón admitidos al Lying-In Hospital y 43 hermanos o hermanas de miembros reumáticos de la Clínica Cardíaca.

Cuarenta de los 121 pacientes de familias geneticamente susceptibles desarrollaron fiebre reumática comparados con 3 de 525 niños de familias no susceptibles.

Análisis genético de los varios tipos de apareamiento produjo buena concordancia con herencia recesiva sencilla a la vez que excluyo otros mecanismos. Corroboración de la conclusión previa que la susceptibilidad a la fiebre reumática se hereda como un rasgo sencillo recesivo se obtuvo.

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REFERENCES

[1] Wilson, M. G., and Schweitzer, M. D.: Rheumatic fever as a familial disease. Environment, communicability and heredity in their relation to the observed familial incidence of the disease. J. Clin. Invest. **16:** 555, 1937.

[2] —, —, and Lubschez, R.: The familial epidemiology of rheumatic fever: genetic and epidemiologic studies. J. Pediat. **22:** 468, 1943.

[3] Gray, F. G., Quinn, R. W., and Quinn, J. P.: A long-term survey of rheumatic and nonrheumatic families. With particular reference

to environment and heredity. Am. J. Med. **13:** 400, 1952.

[4] UCHIDA, I. A.: Possible genetic factors in the etiology of rheumatic fever. Am. J. Human Genetics **5:** 61, 1953.

[5] STEVENSON, A. C., AND CHEESEMAN, E. A.: Heredity and rheumatic fever. A study of 462 families ascertained by an affected child and 51 families ascertained by an affected mother. Ann. Eugenics **17:** 177, 1953.

[6] Immunologic and biochemical studies in infants and children with special reference to rheumatic fever.

[a] WILSON, M. G.: I. The role of genetic susceptibility. Pediat. **2:** 239, 1948.

[b] DEGARA, P. F., AND GOLDBERG, H. P.: II. Complement titers in normal conditions. Pediatrics **2:** 242, 1948.

[c] —, AND —: III. Complement titers in abnormal conditions. Pediatrics **2:** 248, 1948.

[d] —: IV. Occurrence of agglutinins in normal and abnormal conditions. Pediatrics **2:** 410, 1948.

[e] LUBSCHEZ, R.: V. Electrophoretic patterns in blood plasma and serum in normal children. Pediatrics **2:** 570, 1948.

[f] WILSON, M. G., AND LUBSCHEZ, R.: VI. Electrophoretic patterns of blood plasma and serum in rheumatic children. Pediatrics **2:** 577, 1948.

[g] EPSTEIN, N., LUBSCHEZ, R., DEGARA, P. F., AND WILSON, M. G.: VII. Inhibition of hyaluronidase by sera. Pediatrics **4:** 569, 1949.

[h] HAIN, K., AND WILSON, M. G.: VIII. Response to pituitary adrenocorticotropic hormone (ACTH). Pediatrics **4:** 579, 1949.

[7] EPSTEIN, N.: The incidence and frequency of infections at specific ages in infancy and childhood: with special reference to upper respiratory infections in potentially rheumatic susceptible children. Am. J. Dis. Child. (In press)

[8] WILSON, MAY G.: Rheumatic Fever. New York, The Commonwealth Fund, 1940.

[9] —, EPSTEIN, N., HELPER, H. N., AND HAIN, K.: Evaluation of routine serial fluoroscopic examinations of the heart in the postero-anterior and oblique views at specific degrees of rotation. Circulation **8:** 879, 1953.

[10] ROBERTS, J. A. F.: An introduction to medical genetics, London, Humphrey Milford, 1940.

The Presence of Venoarterial Shunts in Patients with Interatrial Communications

By H. J. C. Swan, M.B., Ph.D., M.R.C.P. (Lond.), Howard B. Burchell, M.D., and Earl H. Wood, M.D., Ph.D.

Evidence is presented which indicates that shunting of small amounts of blood from right to left occurs frequently through interatrial communications. Such right-to-left shunts are of small magnitude in the usual case of atrial septal defect, but it appears that of the fractions of blood shunted, a greater proportion has originated from the inferior vena cava than from the superior vena cava.

In the majority of cases of uncomplicated atrial septal defect the major hemodynamic change is an arteriovenous (left-to-right) shunt of considerable magnitude. Because cyanosis or significant desaturation of the systemic arterial blood is uncommon, a shunt in the opposite direction (venoarterial, or right-to-left) is now considered unusual in this condition.[1, 2] In certain reports, which included a number of atypical cases[3] or cases in which the complete diagnosis was not clearly established,[4] significant arterial desaturation has been noted.

The oxygen saturation of the systemic arterial blood determined by manometric methods in normal persons has been found to average 97.6 per cent with a range of analytic values of from 94 to 101 per cent.[5] This variability in normal subjects may preclude the detection of venoarterial shunts of less than 15 per cent of systemic flow on the basis of desaturation of the systemic arterial blood. When significant arterial desaturation due to a venoarterial shunt is found, an additional structural anomaly or pulmonary hypertension or cardiac failure, singly or in combination, is likely to be present. Right-to-left shunts may frequently be associated with pulmonary stenosis with intact ventricular septum and occur through a "valve-competent," patent, foramen ovale[6] or through a coexistent atrial septal defect. The term "interatrial communication" is used to include all direct pathways between the atria, normal and abnormal.

The demonstration of the presence and site of a communication through which a right-to-left shunt is occurring, by dilution curves of T-1824, is now an established technic.[7-10] In this paper, evidence will be presented which indicates that shunting of small amounts of blood from right to left occurs frequently through interatrial communications. Such right-to-left shunts are of small magnitude in the usual case of atrial septal defect but it appears that of the fractions of blood shunted, a greater proportion has originated from the inferior vena cava than from the superior vena cava.

Methods

Dilution curves of T-1824 were obtained following injection of dye into both the inferior and the superior vena cava in four patients with uncomplicated atrial septal defect, three patients with persistent common atrioventricular canal, one patient with atrial septal defect and mitral stenosis, one patient with anomalous pulmonary venous connection of the right lung and a small atrial septal defect, one patient with pulmonary stenosis, intact interventricular septum and valve-competent foramen ovale and one patient with pulmonary stenosis, intact interventricular septum and atrial septal defect. In an additional patient with atrial septal defect, dilution curves were obtained, but the instant of injection of T-1824 was not indicated on the record; hence these curves have not been included in this series, although they did not differ in general appearance from the curves obtained in the majority of other patients.

Each patient was studied as completely as possible by the cardiac catheterization technic[11-13] to establish the nature of the anomaly present. Dilution curves were recorded photographically, utilizing

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earpiece oximeters attached to both ears and a cuvette oximeter[14] connected to a 20-gage needle in the right radial artery. The dilution curves were obtained while the patients breathed 100 per cent oxygen and, in some instances, while they breathed room air. Injections of dye were made through the cardiac catheter into the inferior vena cava 1 to 3 cm. below the diaphragm and into the superior vena cava a short distance cephalad to its junction with the right atrium. A number 6, or less frequently a number 5 or number 7, Cournand bird's-eye tip catheter was used and the selected dose of dye (in a volume of 1.5 or 2.0 cc.) was injected as rapidly as possible (one to two seconds). This was followed immediately by a further injection of 5 cc. of isotonic saline solution. In these patients dilution curves were also recorded following injection of T-1824 into right or left pulmonary arteries or into the main pulmonary trunk, or into all of these vessels. The systemic and pulmonary flows were calculated, when possible, both when air and when oxygen was being breathed. For estimations of pulmonary flow (liters per minute) the oxygen consumption (in cubic centimeters per minute) was divided by the difference between the oxygen content of blood in the pulmonary vein (assumed to equal 98 per cent of the oxygen capacity, in cubic centimeters per liter of blood + 3.0 cc.) and the oxygen content of blood in the pulmonary artery (in cubic centimeters per liter of blood), as estimated by the method of Van Slyke and Neill.[15] For estimations of systemic flow (liters per minute) the oxygen consumption (in cubic centimeters per minute) was divided by the difference between the oxygen content of radial-artery blood and the content of mixed venous blood. The latter value ($S_{\bar{v}}$) was calculated from the relationship,

$$S_{\bar{v}} = \frac{S_{vs} + 2S_{vi}}{3} \times O_2 \textit{ capacity},$$

in which S_{vs} = per cent saturation of superior vena caval blood and S_{vi} = per cent saturation of inferior vena caval blood, in each instance determined by cuvette oximeter, and in which $S_{\bar{v}}$ and O_2 capacity are expressed as cubic centimeters of oxygen per liter of blood.

The oxygen saturation of radial-artery blood was determined while the patient breathed room air according to the formula,

$$O_2 \textit{ saturation (air)} = \frac{O_2 \textit{ content} - 0.3}{O_2 \textit{ capacity}} \times 100$$

in which saturation is expressed as a percentage, and content and capacity in cubic centimeters per 100 cc. of blood.

When the patient breathed 100 per cent oxygen the saturation of the radial-artery blood was considered to be 100 per cent if the oxygen content exceeded the capacity by more than 1 volume per cent. The oxygen tension required to produce this concentration of dissolved oxygen is equivalent to or exceeds the oxygen tension of 400 mm., expressed in terms of mercury, required to produce practically complete saturation of hemoglobin with oxygen.[1] When the physically dissolved oxygen was less than 1 volume per cent of the oxygen, saturation was estimated from the oxygen tension (calculated on the basis of the quantity of oxygen in physical solution)* by reference to the oxygen dissociation curve established at high levels of oxygen pressure (pO_2) by Nahas and colleagues.[16]

Results

In the table the major hemodynamic findings in each case are given, together with certain data from dilution curves of T-1824 following its injection into the superior and the inferior vena cava and into the right ventricle or right, left or main pulmonary artery.

The two patients with pulmonary stenosis (cases 2 and 3) both showed considerable elevation of the right ventricular pressure while in one case of atrial septal defect (case 7) the pressure in the right ventricle exceeded that in the pulmonary artery by more than 20 mm. Hg. In neither of the former patients was it possible to demonstrate significant left-to-right shunting of blood on the basis of repeated sampling of blood from the right side of the heart; however, in case 3 following injection of dye into the pulmonary trunk the contour of the dye-dilution curve indicated that indeed a left-to-right shunt of small magnitude was present. It has been found in this laboratory that dye-dilution curves recorded following injections of dye directly into the central circulation may permit the recognition of left-to-right shunts when the relations of the oxygen saturation of blood drawn from different locations in the right atrium and both venae cavae are within normal limits.[18] In regard to the moderate difference between the systolic pressures in the pulmonary artery (case 7) and those in the right ventricle, it is

* *Approximate* O_2 *tension*

$$= \frac{(B - 47) \cdot (O_2 \textit{ content} - O_2 \textit{ capacity})}{100 \cdot \alpha 38^\circ},$$

in which B = barometric pressure (mm. of Hg), and $\alpha\ 38^\circ$ = solubility coefficient for oxygen at 38 C = 0.0209 + 0.000108 (volume per cent oxygen capacity).

not possible to be certain whether or not this patient has a congenital pulmonary stenosis of mild degree in addition to an atrial septal defect, since significant differences between these pressures occur frequently in patients with atrial septal defect.[19]

In three of the nine patients without pulmonary stenosis a diagnosis of persistent common atrioventricular canal was made after cardiac catheterization. This condition must always be considered in the differential diagnosis of atrial septal defect. In these three patients the oxygen-saturation data indicated a source of moderate arterialization in the right ventricle in addition to the arterialization in the atrium. In each patient the catheter was passed from the right atrium to the left ventricle and the position of its shaft lay in the axis of the coronary sinus, giving rise to an unusual but, for this condition, typical radiologic appearance.

The dilution curves recorded following injection of T-1824 into the superior and the inferior vena cava while the patients breathed 100 per cent oxygen are reproduced for patients 1 to 8 in figure 1. In each instance there is evidence of a right-to-left shunt when the injection of dye is made into the inferior vena cava, although in case 8 this consists only of an abnormal rounding of the initial part of the dilution curve. The appearance time of these curves is less than the appearance time of dye injected at a more central site (table),

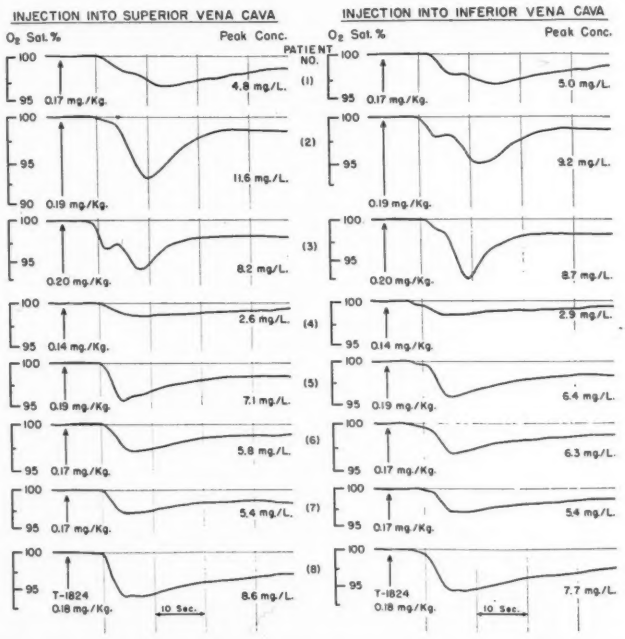

FIG. 1. Dilution curves of T-1824 recorded by earpiece oximeters following injection of indicator into superior vena cava (left panel) and inferior vena cava (right panel) in patients 1 to 8 with interatrial communications, recorded while 100 per cent oxygen was being breathed. For each dilution curve the instant of injection is represented by the vertical arrow below which the amount of dye injected is indicated. The oxygen saturation scale to the left of each panel is a measure of the relative sensitivity of the recording instrument for each subject, and the peak concentration of dye is indicated to the right of each panel. In the curves for patients 1 to 3 in the left panel the initial break in the dilution curve indicates the shunting of a portion of superior caval blood in the right-to-left direction. In the right panel an initial break is present in all curves indicating that a right-to-left shunt of inferior caval blood was present in all these patients. Note that only in case 3 does the magnitude of the shunt of superior caval blood exceed that of inferior caval blood.

TABLE 1.—*Hemodynamic Data Obtained During Cardiac Catheterization of 11 Patients with Interatrial Communications*

Case	Diagnosis	Age, sex	Surface area, meters²	Patient breathing	Pressure, mm. of Hg				Flow L./min./M.²		Radial artery blood oxygen				Dye-dilution data†‡									
					Pulm. art. wedge	Pulm. art.	Right vent.	Right atrium	Pulm.	Syst.	Content cc./100 cc.	Capacity cc./100 cc.	Saturation, %	Dissolved O_2, cc./100 cc.	More proximal site				Superior vena cava			Inferior vena cava		
															Site	AT (Seconds)	PCT (Seconds)	R-L, %	AT (Seconds)	PCT (Seconds)	R-L, %	AT (Seconds)	PCT (Seconds)	R-L, %
1	ASD, mitral stenosis*	23 F	1.66	Air	26/16	34/16	34/8	21/9	12.3	1.7	17.7	19.0	92	—	—	—	—	—	—	—	—	—	—	—
				100% O_2	—	33/15	34/8	17/7	13.4	1.8	19.9	18.8	100	1.1	RV	11.2	16.0	Nil	7.3	20.0	24.0	8.3	21.1	22
2	Pulm. stenosis, probe-patent foramen ovale*	21 F	1.6	Air	—	13/8	149/15	16/5	2.4	2.7	15.4	16.2	93	—	—	—	—	—	—	—	—	—	—	—
				100% O_2	8/3	13/7	170/12	11/5	2.7	3.0	17.5	16.6	99	0.9	LPA	7.0	13.0	Nil	5.3	16.7	6.0	6.4	18.5	17
3	ASD, pulm. stenosis*	20 F	1.53	Air	12/6	21/11	110/4	7/3	3.2	4.1	14.4	15.4	92	—	—	—	—	—	—	—	—	—	—	—
				100% O_2	—	12/7	108/7	4/0	3.1	4.3	16.1	15.4	99	0.7	RV	7.3	13.1	Nil	5.4	15.7	22.0	7.9	16.6	6
4	Persistent common atrioventricular canal	5 F	0.8	Air	—	27/10	30/−2	4/−2	6.3	2.4	15.3	15.6	96	—	—	—	—	—	—	—	—	—	—	—
				100% O_2	9/4	26/8	27/−1	4/−2	—	—	17.1	15.7	100	1.4	PT	6.0	12.4	Nil	6.4	15.5	3.0	4.9	11.4	15
5	ASD*	24 F	1.7	Air	11/8	17/8	25/2	7/4	17.7	4.2	16.3	16.5	97	—	—	—	—	—	—	—	—	6.0	13.8	5
				100% O_2	—	24/9	—	8/5	8.8	3.9	18.1	16.4	100	1.7	RPA	6.3	10.5	Nil	6.7	13.0	Nil	5.0	12.6	6
6	Persistent common atrioventricular canal*	27 F	1.56	Air	—	23/8	26/4	8/5	8.9	2.8	17.2	17.3	98	—	—	—	—	—	—	—	—	4.9	13.8	4
				100% O_2	10/7	27/6	32/5	9/5	—	3.1	18.8	17.3	100	1.5	PT	5.3	10.1	Nil	7.0	12.2	Nil	4.4	14.0	5
7	ASD	16 F	1.75	Air	10/4	25/10	47/8	11/5	5.4	2.4	17.0	17.2	97	—	—	—	—	—	—	—	—	—	—	—
				100% O_2	—	24/10	48/10	11/5	—	2.3	19.2	17.3	100	1.9	PT	6.2	11.5	Nil	7.3	14.5	Nil	5.2	13.3	5
8	ASD, pericarditis	31 F	1.61	Air	27/20	50/25	46/19	26/19	9.5	4.8	11.3	11.3	98	—	—	—	—	—	—	—	—	—	—	—
				100% O_2	—	49/27	48/18	15/10	11.6	3.0	13.1	11.5	100	1.6	LPA	4.4	8.8	Nil	5.8	11.2	Nil	4.1	12.1	4
9	Persistent common atrioventricular canal	30 F	1.60	Air	8/5	27/10	29/4	7/4	11.6	3.5	16.7	17.4	94	—	—	—	—	—	—	—	—	4.5	13.9	12
				100% O_2	—	22/7	—	4/0	10.2	3.2	18.8	17.1	100	1.7	PT	6.3	10.3	Nil	7.6	15.5	Nil	5.1	14.5	9
10	ASD, anom. pulm. ven. connection*	23 M	1.98	Air	11/8	27/14	28/5	6/3	8.4	2.8	20.0	20.7	95	—	—	—	—	—	—	—	—	10.1	14.0	Nil
				100% O_2	—	26/13	30/5	9/4	9.0	3.1	—	—	—	—	PT	6.0	9.7	Nil	7.0	11.0	Nil	6.7	11.8	Nil
11	ASD	19 F	1.68	Air	17/9	21/8	30/4	7/3	9.2	4.7	16.6	17.1	96	—	RPA	4.3	8.2	Nil	6.6	11.7	Nil	6.0	12.3	Nil
				100% O_2	—	—	—	—	—	—	18.7	17.1	100	1.6	—	—	—	—	—	—	—	—	—	—

* Catheterization diagnosis confirmed during surgical correction of the anomaly (Dr. John W. Kirklin).

† Recorded by ear oximeter.

‡ Abbreviations:[17] AT, appearance time; PCT, peak concentration time; RPA, right pulmonary artery; LPA, left pulmonary artery; PT, pulmonary trunk; RV, right ventricle.

indicating that the shunt in question occurs at atrial level.

In 7 of the total of 11 patients the dilution curves following injection of dye into the superior vena cava did not indicate the presence of a right-to-left shunt and in two patients there was no evidence of a right-to-left shunt from either cava. In the remaining patients the initial hump of the curve following injection into the superior vena cava was greater than the initial hump following injection into the inferior vena cava in one case, equal to it in one case, and smaller in two cases. Thus in 9 of the 11 patients a right-to-left shunt could be demonstrated, and further in seven of these patients the proportion of inferior vena-caval blood shunted right to left through the atrial defect was larger than that from the superior vena cava.

A method of analysis of dilution curves whereby the magnitude of right-to-left shunts may be estimated has recently been described.[8] An assumption basic to this method is that complete mixing of indicator with the blood has occurred before the mixture of blood and indicator reaches the site of the defect. The evidence presented in this paper indicates that this condition is not fulfilled in the case of right-to-left shunt through an interatrial communication, for in all but one instance the proportion of indicator shunted right to left differed obviously between the caval injection sites (fig. 1). However, in the absence of a more acceptable method of analysis the volume of right-to-left shunt has been calculated according to the method of Swan and associates,[8] recognizing the possibility of appreciable error in certain values. Nevertheless

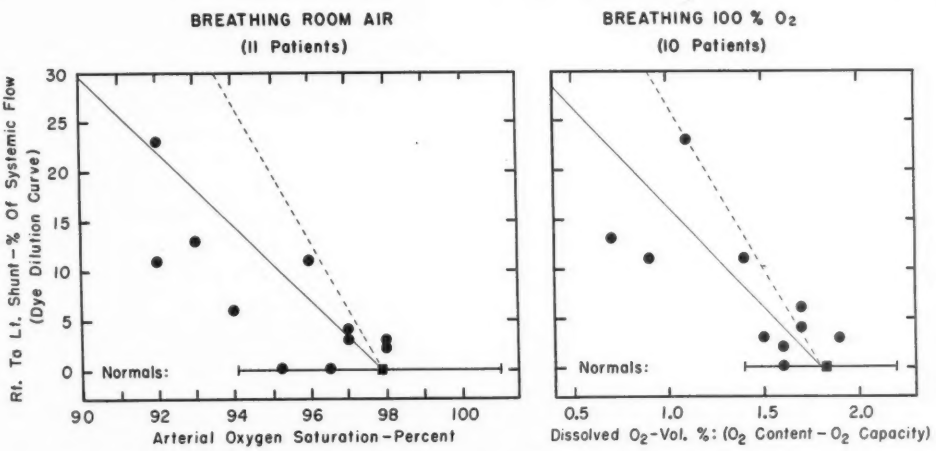

FIG. 2. Relation of the magnitude of right-to-left shunt determined from dye-dilution curves to systemic arterial saturation (left panel, 11 patients breathing room air) and to volume of oxygen in physical solution in arterial blood (right panel, 10 patients breathing 100 per cent oxygen). The average of the shunts ($\bar{S}$) from the superior and the inferior cava was calculated thus: $\bar{S} = \frac{S_{vs} + 2S_{vi}}{3}$, in which S_{vs} is the shunt from superior vena cava and S_{vi} the shunt from the inferior vena cava (table 1). The solid squares represent the average values for normal subjects,[5] and the range is indicated. The diagonal lines represent the calculated relation of the systemic arterial saturation to the volume of right-to-left shunt. These lines were estimated on the basis of the average oxygen capacity (16.7 volumes per 100 cc. of blood) and the arteriovenous difference (4.9 volumes per 100 cc. of blood) found in the group studied. In each panel the solid line represents the relationship which would pertain if the oxygen saturation of the shunted blood were the same as that of mixed venous blood (71 per cent for room-air data and 83 per cent when the patients breathed 100 per cent oxygen), and the dashed line the relationship if the saturation of the shunted blood were the same as that of pulmonary-artery blood (78 per cent and 92 per cent respectively when the patients breathed air and 100 per cent oxygen).

‡ Abbreviations: AT, appearance time; RV, right ventricle.

it is thought that the values probably indicate the approximate magnitude of the right-to-left shunt in most instances.

By use of these calculations it may be shown (fig. 2) that the magnitude of the right-to-left shunt is inversely related to the volume of oxygen in physical solution in arterial blood when the patient is breathing 100 per cent oxygen and to the systemic arterial saturation when the patient breathes air. Small shunts (less than 10 per cent) are associated with a normal complement of physically dissolved oxygen (1.4 to 2.2 volumes per 100 cc. of blood)[5] when the patient is breathing oxygen and with normal arterial saturations (94 to 101 per cent)[5] when he is breathing air. When the volume of dissolved oxygen is less than 1.5 volumes per cent during the breathing of oxygen and the arterial saturation is less than 94 per cent during the breathing of air, right-to-left shunts of greater magnitude are found.

Comment

It is of interest that in 9 of the 11 cases studied the dilution curves recorded following injections of dye into the inferior and the superior vena cava indicated the presence of a right-to-left shunt through the defect in the atrial septum. In five of the nine cases the shunt was demonstrable only from the inferior vena cava, and in these instances the total venoarterial shunt was small.

In cases 4 to 11 the clinical features were considered to indicate a diagnosis of atrial septal defect, with the addition that a coincidental pericarditis was present in case 8. Use of currently available cardiac catheterization technics[12, 13] permitted a more nearly complete diagnosis in several instances.

The findings reported above indicate that, although a right-to-left shunt is frequently present, it is of small magnitude in the usual case of atrial septal defect, which is in keeping with the more generally accepted view concerning this condition. In two of the four cases with moderate shunts, pulmonary stenosis was present, while in the remaining two cases the anomalies were not simple.

Two important facts may be noted. First, these developments of the dye-dilution technic offer a highly sensitive method for the demonstration of right-to-left shunts. In its more general application the method permits the certain identification of an interatrial communication in the absence of a significant left-to-right shunt. Second, for relatively small right-to-left shunts (3 to 15 per cent of systemic flow) these methods allow for approximate quantitation of their magnitude when even demonstration on the basis of oxygen-saturation data may be impossible. It must be pointed out, however, that the arterial dilution curves are produced by complex dilution and mixing processes which cannot be accurately quantitated at present. Hence attempts at more precise quantitation of the magnitude of shunts demonstrated by the technic are of questionable value at this time.

In the majority of cases a greater shunt was demonstrated to occur from the inferior than from the superior vena cava. In case 3 the shunt occurring from the superior vena cava was of considerably greater magnitude than that from the inferior vena cava. This finding was at variance with the results in the other cases and cannot be adequately explained. On the basis of past experience,[20, 21] it was thought to indicate a defect lying in the cephalic part of the atrial septum, but in fact at operation the defect was found in the region of the foramen ovale.

Using angiocardiographic technics, Lind and Wegelius[22] observed in patients with atrial septal defect and in normal newborn infants that some of the contrast medium injected into the inferior vena cava passed into the left atrium but returned from this chamber to the right atrium. As a possible explanation for their findings these workers suggested that the sudden injection of contrast medium increased the volume and pressure in the right side of the heart, and hence a transient right-to-left shunt occurred. It is unlikely that such an explanation pertains to the present findings, for the volume injected was small (1 to 2.0 cc. of dye, followed by 5 cc. of saline solution) in relation to the volume of blood returning to the heart.

The usual direction of flow across an atrial septal defect has been ascribed to the differ-

ences in pressure between the atria first demonstrated in man by Cournand.[23] Calazel and co-workers[24] found that a pressure gradient existed between right and left atria in patients with moderate to large venoarterial shunts. An arteriovenous shunt was present in patients with a gradient from left atrium to right atrium. In the latter group a transient reversal of this pressure gradient at the beginning of atrial filling was demonstrated, which was thought to cause a small venoarterial shunt. Little and associates[25] measured simultaneously the left and the right atrial pressure in dogs before and after the creation of atrial septal defects. They found that a pressure gradient existed from left atrium to right atrium even when relatively large (5 to 8 mm.) defects were created. This difference was abolished and a reverse gradient was created for certain phases of the cardiac cycle when the pulmonary artery was acutely constricted.

In the usual case of atrial septal defect (valve incompetent foramen ovale) in man it may not be possible to demonstrate a significant difference between the pressure levels in the right and left atria.[19] In such cases the pattern and direction of inflow and outflow streams through the atria may be related at least in part to the shunts which occur. It has been demonstrated that mixing of blood from the left and right lungs in the left atrium is incomplete in the great majority of patients with atrial septal defect, for a greater proportion of blood from the right lung is shunted to the right atrium while a greater proportion of blood from the left lung passes to the systemic circulation.[20] When the blood flow through the right atrium is large, the atrium may function during diastole more as a channel than as a storage chamber. Blood streams from the superior and the inferior vena cava and from each lung may traverse this channel to the respective ventricles while still retaining a certain degree of identity.

Barclay, Franklin and Prichard[26] found that the greater part of a contrast medium injected into the "posterior caval channel" (inferior vena cava) of lambs in the late fetal period passed into the left atrium, while all of the contrast medium reaching the heart by way of the "anterior caval channel" (superior vena cava) passed to the right ventricle. If the inferior vena cava is cut across and viewed from below in the heart of a patient who has died from a cardiac or noncardiac cause, the limbus of the fossa ovalis can be seen to straddle the atrial orifice of the inferior cava so that a portion of the inflow from the inferior cava impinges directly on the floor of the fossa ovalis (fig. 3). Thus when the valve of the foramen (septum primum) is not fused to the septum secundum or when a true defect in this location exists, the blood from the inferior vena cava could pass equally well into either the right or the left atrium. The small left-to-right pressure gradient which usually exists between the atria results in a left-to-right shunt and apparently prevents the flow of all but a small part of the inferior caval blood into the left atrium in most patients. In contrast to that of the inferior vena cava the atrial orifice of the superior vena cava is usually directed toward the tricuspid valve. The direct stream of flow from the superior cava therefore would not appear to pass in as close a relation to the fossa ovalis and defects thereof as would blood from the inferior vena cava.

The relative proportions of blood shunted from each caval site should depend on the proximity of the stream under consideration to the defect and hence should permit the site of the defect to be predicted. This has been conclusively demonstrated by Silver and co-workers[21] who created defects in the atrial septum of dogs which were subsequently studied by the dye-dilution technic. The pattern of the dilution curves recorded following injection of dye into the lobar branches of the right pulmonary artery, the left pulmonary artery and the inferior and the superior vena cava was found to indicate correctly the approximate location of the defect in the atrial septum. This has also been found to be true in human patients. In case 1 the dilution curves indicated that the atrial defect lay in the same relationship to the flow from both the inferior and the superior vena cava. In cases 2, 5 and 6 the defect was thought to lie more closely in relation to the inferior than to the superior vena cava. When surgical correction was

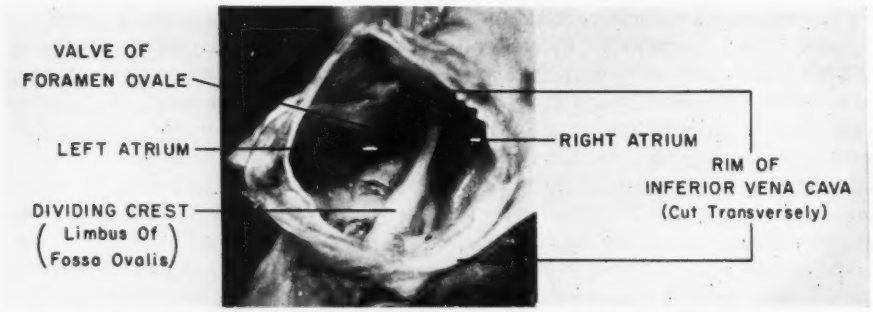

FIG. 3. The interior of the heart viewed from the inferior vena cava in a 4 month old infant with total anomalous pulmonary venous drainage and valve-competent foramen ovale. Note the position of the muscular ridge derived from the septum secundum. This has been termed the "dividing crest" by Barclay and co-workers,[26] and separates the left from the right atrium. The structure lying to the left of the dividing crest, the valve of the foramen ovale, is derived from the septum primum and when it is deficient or when the foramen ovale is very large, a free communication (valve-incompetent foramen ovale) exists between the atria. This gives rise to the usual type of atrial septal defect. When the valve is of sufficient size to close the foramen ovale but fails to fuse with it, a potential pathway from the right to left atrium exists, but, in the presence of normal pressure relationships, no path exists from the left to the right atrium (valve-competent foramen ovale). (Specimen provided through the courtesy of Dr. J. E. Edwards.)

undertaken in these patients (Dr. J. W. Kirklin) the locations of the defects were found to be as predicted. In case 11 no right-to-left shunt was demonstrated, but a small atrial septal defect was found in association with anomalous venous connection of the right lung. In case 3 the dilution curves suggested that the defect was located in close relation to the superior vena cava but an atrial septal defect of moderate size was found in the region of the fossa ovalis.

SUMMARY

Dilution curves of T-1824 have been recorded by the oximeter technic in 11 patients with interatrial communications, following injection of the dye into both the inferior and the superior vena cava. In 9 of 11 cases a right-to-left shunt could be demonstrated when dye was injected into the inferior vena cava. In the seven cases in whom no shunt occurred from the superior vena cava, the oxygen saturation of systemic arterial blood was normal, and the amount of oxygen in physical solution in the blood when the patient was breathing 100 per cent oxygen exceeded 1.5 volumes per cent. In the remaining patients the shunt was found to occur also from the superior vena cava, and the physically dissolved oxygen was less than 1.5 volumes per cent. The existence of such right-to-left shunts is probably associated with the relation of the septal defect to the stream of blood passing from either vena cava to the right ventricle. In four of the five cases in which successful surgical correction was carried out, the approximate site of the defect was correctly predicted.

SUMARIO ESPAÑOL

Curvas de dilución de T-1824 han sido registradas por la técnica del oxímetro en 11 pacientes con comunicaciones interatriales, luego de la inyección del tinte en la vena cava superior e inferior. En 9 de 11 casos un "shunt" de derecha a izquierda se pudo demostrar cuando el tine fué inyectado en la vena cava inferior. En los siete casos en los cuales un "shunt" no ocurrió de la vena cava superior, la saturación de oxígeno de la sangre arterial sistémica fué normal y la cantidad de oxígeno en solución física en la sangre cuando el paciente estaba respirando oxígeno al 100 por ciento excedió 1.5 volumenes por ciento. En el restante de los pacientes el "shunt" se encontró ocurrir también de la vena cava superior y el oxígeno en solución física fué menos de 1.5 volumenes por ciento. La existencia de tal "shunt" de derecha a izquierda esta probablemente asociada a l

relación del defecto septal al chorro de sangre pasando de una de las vena cavas al ventrículo derecho. En cuatro de los cinco casos en que se efectuó corrección quirúrgica con éxito, el lugar aproximado del defecto se pudo predecir.

REFERENCES

[1] Barber, J. M., Magidson, O., and Wood, P.: Atrial septal defect: With special reference to the electrocardiogram, the pulmonary artery pressure and the second heart sound. Brit. Heart J. **12:** 277, 1950.

[2] Chapman, C. B., and Fraser, R.: Clinical and hemodynamic features of uncomplicated interatrial defect in adults. Am. Heart J. **46:** 352, 1953.

[3] Taylor, B. E., Geraci, J. E., Pollack, A. A., Burchell, H. B., and Wood, E. H.: Interatrial mixing of blood and pulmonary circulatory dynamics in atrial septal defects. Proc. Staff Meet., Mayo Clin. **23:** 500, 1948.

[4] Cosby, R. S., Griffith, G. C., Zinn, W. J., Levinson, D. C., Dimitroff, S. P., Oblath R. W., and Jacobson, G.: Cardiac catheterization in interatrial septal defect. Am. J. Med. **14:** 4, 1953.

[5] Wood, E. H.: Normal oxygen saturation of arterial blood during inhalation of air and oxygen. J. Appl. Physiol. **1:** 567, 1949.

[6] Maraist, F., Daley, R., Draper, A., Jr., Heimbecker, R., Dammann, F., Jr., Kieffer, R., Jr., King, J. T., Ferencz, C., and Bing, R. J.: Physiological studies in congenital heart disease. X. The physiological findings in thirty-four patients with isolated pulmonary valvular stenosis. Bull. Johns Hopkins Hosp. **88:** 1, 1951.

[7] Nicholson, J. W., III, Burchell, H. B., and Wood, E. H.: A method for the continuous recording of Evans blue dye curves in arterial blood, and its application to the diagnosis of cardiovascular abnormalities. J. Lab. & Clin. Med. **37:** 353, 1951.

[8] Swan, H. J. C., Zapata-Diaz, J., and Wood, E. H.: Dye dilution curves in cyanotic congenital heart disease. Circulation **8:** 70, 1953.

[9] —, and Wood, E. H.: Localization of cardiac defects by dye-dilution curves recorded after injection of T-1824 at multiple sites in the heart and great vessels during cardiac catheterization. Proc. Staff Meet., Mayo Clin. **28:** 95, 1953.

[10] —: Diagnostic applications of indicator dilution curves in heart disease. Minnesota Med. **37:** 123, 1954.

[11] Wood, E. H.: Special instrumentation problems encountered in physiological research concerning the heart and circulation in man. Science. n.s. **112:** 707, 1950.

[12] Symposium on cardiac catheterization. II. Proc. Staff Meet., Mayo Clin. **25:** 41, 1950.

[13] Symposium on cardiac catheterization. III. Proc. Staff Meet., Mayo Clin. **28:** 49, 1953.

[14] Wood, E. H.: Oximetry. In: Glasser, O. Medical Physics. Chicago, The Year Book Publishers, 1950. Vol. 2, pp. 664–680.

[15] Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. J. Biol. Chem. **61:** 523, 1924.

[16] Nahas, G. G., Morgan, E. H., and Wood, E. H.: Oxygen dissociation curve of arterial blood in men breathing high concentrations of oxygen. J. Appl. Physiol. **5:** 169, 1952.

[17] Wood, E. H., and Swan, H. J. C.: Definition of terms and symbols for description of circulatory indicator-dilution curves. J. Appl. Physiol. **6:** 797, 1954.

[18] Swan, H. J. C., and Wood, E. H.: Differences between dilution curves recorded following injections of T-1824 into right and left pulmonary arteries in cases of atrial septal defect. Unpublished data.

[19] Weidman, W. H., Swan, H. J. C., and Wood, E. H.: A hemodynamic study of 60 cases of atrial septal defect without associated cardiac anomalies. Unpublished data.

[20] Swan, H. J. C., Burchell, H. B., and Wood, E. H.: Differential diagnosis at cardiac catheterization of anomalous pulmonary venous drainage related to atrial septal defects or abnormal venous connections. Proc. Staff Meet., Mayo Clin. **28:** 452, 1953.

[21] Silver, A. W., Swan, H. J. C., and Kirklin, J. W.: Demonstration by dye dilution technics of preferential flow across atrial septal defects from right pulmonary veins and inferior vena cava. (Abstr.) Federation Proc. **13:** 138, 1954.

[22] Lind, J., and Wegelius, C.: Atrial septal defects in children: An angiocardiographic study. Circulation **7:** 819, 1953.

[23] Cournand, A., Motley, H. L., Himmelstein, A., Dresdale, D., and Baldwin, J.: Recording of blood pressure from the left auricle and the pulmonary veins in human subjects with inter-auricular septal defect. Am. J. Physiol. **150:** 267, 1947.

[24] Calazel, P., Gerard, R., Daley, R., Draper, A., Foster, J., and Bing, R. J.: Physiological studies in congenital heart disease. XI. A comparison of the right and left auricular, capillary and pulmonary artery pressures in nine patients with auricular septal defect. Bull. Johns Hopkins Hosp. **88:** 20, 1951.

[25] Little, R. C., Opdyke, D. F., and Hawley, J. G.: Dynamics of experimental atrial septal defects. Am. J. Physiol. **158:** 241, 1949.

[26] Barclay, A. E., Franklin, K. J., and Prichard, M. M. L.: The foetal circulation: And cardiovascular system, and the changes that they undergo at birth. Oxford, Blackwell Scientific Publications, 1944.

The Effect of Oral Iodide on Serum Butanol-Insoluble Protein-Bound Iodine in Various Species

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It is possible that there is an association between the butanol-insoluble protein-bound iodine developed in plasma when potassium iodide is fed and the reduction of serum and hepatic cholesterol. This fraction constitutes most of the protein-bound iodine increase observed in iodide-fed rabbits, dogs, rats and hypertensive human beings. It appears a few days after iodide feeding is begun and disappears four to eight weeks after discontinuing iodide. The dose required to produce minimum and maximum concentrations has been determined in all of these animals and in men. Further, it was found that hypothyroidism reduced the iodide requirement to one-tenth that necessary to produce comparable amounts of butanol-insoluble protein-bound iodine in normal animals.

ADMINISTRATION of iodide to rabbits fed moderate amounts of cholesterol inhibited hypercholesteremia, reduced hepatic cholesterol and protected against atherosclerosis.[1-6] Large amounts of iodide were required; small amounts had the opposite effect and increased serum and hepatic cholesterol.[5, 6, 7]

These actions of iodine were seemingly independent of the thyroid gland[3, 6] and of the serum butanol-soluble (thyroxine containing) iodine.[6] Depression of serum and hepatic cholesterol in cholesterol-iodide fed rabbits was associated with an increase in the butanol-insoluble fraction of the protein-bound iodine to concentrations of about 20 μg. per 100 ml. Hypothyroidism in rabbits has also been shown to enhance the effectiveness with which small doses of iodide increase the concentration of this fraction, protect against hypercholesterolemia and reduce hepatic cholesterol.[6]

This relationship between the effect of iodide on cholesterol metabolism and the concentration of serum butanol-insoluble iodine prompted study of iodide dosages required to elicit the appearance of detectable concentrations of the butanol-insoluble fraction in man, normal and hypothyroid rabbits, rats, and dogs, and the maximal concentrations attainable in these species.

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METHOD

The total serum protein-bound iodine and/or its butanol-insoluble iodine fraction were determined as previously described.[6]

The rabbits were young, mature, New Zealand White males and females weighing approximately 2.5 kg., they were fed rabbit pellets. Iodide was fed six times a week. Rabbits in the first three groups received 16 mg. iodine per kilogram as potassium iodide daily; in the fourth, 32 mg.; and the fifth, 188 mg. (table 2). Iodine in the form of Organidin* was given three rabbits in the third group. Blood was sampled at intervals of 3 to 16 weeks.

Two male and one female dogs were fed dog chow and one fourth pound of horse meat daily and iodide as indicated in table 2. Blood samples were obtained at intervals of a few days to 12 weeks.

Mature male and female rats, 2½ months old, weighing 150 to 200 Gm., were fed a modified Sherman diet for 12 weeks. This consisted of 25 per cent dried whole milk, 67 per cent whole wheat flour, 5 per cent yeast, 2 per cent sodium chloride and 1 per cent calcium lactate. The basal diet contained 0.07 mg. of iodine per kilogram. Potassium iodide was added to supply the following iodine content: (a) 0.07 mg. (b) 0.7 mg. (c) 7.0 mg. (d) 70 mg. per kilogram of diet. The average daily food intake was 21 Gm. per rat, so that the animals in groups (a) and (b) received less than 0.1 mg. iodine per kilogram, (c) 0.8 mg. and (d) 8 mg. Weights were re-

* Organidin is a brand of iodopropylidene glycerol, kindly supplied by Mr. Chiappini of Henry K. Wampole Company.

corded weekly; pooled serum samples were obtained at 12 weeks by exsanguination.

Nine people who had been under treatment for hypertension in the Research Division for some time were given iodide. One woman received 7 mg. iodine per kilogram for six weeks; one man, 13 mg. for five months; one woman, 14 to 24 mg. for three weeks; two men and four women, 35 to 40 mg. for three to eight weeks. Blood samples were taken at two- to three-week intervals (table 3).

Six male dogs were made hypothyroid by intramuscular injection of 20 millicuries I^{131}. They showed no thyroid uptake of a tracer dose (50 microcuries I^{131}) 10 weeks later. The dogs were fed dog chow and ¼ pound horse meat daily, and iodide as indicated in table 4. Dog 9 received 21 to 25 mg. per kilogram for 23 weeks and after a rest period of four months, 33 mg. per kilogram, which was increased in amount every one to two weeks over a period of 12 weeks up to 92 mg. per kilogram. Blood was obtained from all dogs before iodide feeding and at two- to four-week intervals subsequently, and every week from dog 9 while on increasing iodide dosage.

Rats similar to the normal animals used were thyroidectomized. One month later, five groups of 10 males each were given the modified Sherman diet plus iodide for 12 weeks. This contained the same amount of iodine given the normal rats. The average daily food intake was 12 Gm. per animal so that the animals in groups (a) and (b) received less than 0.1 mg. iodine per kilogram of body weight, (c) 0.4 mg., (d) 4 mg., and (e) 20 mg. (diet contained 350 mg. iodine per kilogram). Weights were recorded weekly and pooled serum samples obtained every three weeks.

Results

1. *Serum Protein-bound Iodine Fractions in Normal and Hypothyroid Animals and Hypertensive Patients*

All the serum protein-bound iodine was soluble in butanol at an acid pH in animals receiving no extra iodide. In iodide-fed animals and human beings, there appeared an additional fraction which was insoluble in butanol. As shown in table 1, the total butanol-soluble portion consisted largely, but not entirely, of alkali-insoluble iodine which, in this respect, resembled thyroxine. The concentration of this alkali-insoluble, butanol-soluble fraction was not increased by iodide feeding. Most of the increase in protein-bound iodine in iodide-fed animals and man was butanol-insoluble.

2. *Development and Disappearance of Butanol-Insoluble Iodine*

Butanol-insoluble iodine was present in the blood serum within a few days to a week of feeding potassium iodide and attained a plateau in three weeks (fig. 1). This level was dependent upon the species and amount fed.

The time required for the serum butanol-insoluble iodine to disappear on discontinuing

Table 1.—*Serum Protein-Bound Iodine Fractions in Various Species Fed Potassium Iodide*

Species	Protein-Bound Iodine	Fractions of Protein-Bound Iodine		
		Total Butanol-Soluble	Butanol-Soluble Alkali-Insoluble	Butanol-insoluble
	μg. %	μg. %	μg. %	μg. %
Rabbit, normal*				
no iodide	8.0	8.0	2.8	0
iodide-fed	13.1	7.0	4.6	5.3
	23.8	10.9	4.7	13.2
	46.0	24.0	5.0	25.0
Hypothyroid*				
iodide-fed	9.2	6.0	5.6	4.1
	58.9	14.2	7.3	43.3
Dog, normal				
no iodide	2.0	(2.0)†	2.0	0
Hypothyroid				
no iodide	4.8	(4.8)	—	0
iodide-fed #6	10.2	(7.8)	4.1	2.4
#5	20.6	(14.6)	5.7	6.0
#9	23.5	(6.3)	4.2	17.2
#9	26.5	(9.0)	4.7	17.5
Rat, normal				
no iodide	7.2	(7.2)	6.3	0
iodide-fed	12.0	(9.2)	6.5	2.8
Hypothyroid				
no iodide	2.6	(2.6)	2.0	0
iodide-fed	11.9	(2.2)	2.9	8.7
	25.0	(8.2)	7.2	16.8
Human being				
no iodide "Z"	5.1	(5.1)	3.7	0
iodide-fed "G"	8.3	(6.0)	4.4	2.3
"H"	14.2	(7.2)	7.0	7.6
"C"	16.5	(10.2)	5.8	6.3
"Z"	20.3	(10.2)	4.6	10.1

* Previously published data (6).

† Estimated. Protein-bound iodine minus butanol-insoluble fraction equals total butanol-soluble fraction.

TABLE 2.—*Serum Butanol-Insoluble Iodine and Potassium Iodide Dosage in Normal Animals*

Species and Group No.	No. Animals	Dosage I mg./Kg.	Time Iodide Fed in Weeks	Butanol-Insoluble Iodine		
				μg. %	Range	Average
Rabbit 1	4	16	4–5	27.0	—	
	2		7–8	44.0	—	
2	19		6	32.4	19.8–55.4	
	2		11–12	37.5	36.0–39.0	
3	3		14–16	22.5	17.0–26.0	
	3	(Organidin)		26.5	24.3–31.0	
Rabbit 1, 2, 3 av.		16	4–16		17.0–55.4	32.9
4	4	32	3	46.4	32.6–63.4	
	6		4–5	44.9	37.5–50.0	
	4		11–12	51.3	43.0–56.7	
av.		32	3–12		32.6–63.4	48.2
5	2	188	5–6	32.9		32.9
Rabbits 1–5 av.		16–188	3–16		17.0–63.4	37.1
Dog No.	No. Detns.					
2 (M)	3	3	1–3	(8.4)*	(3.8)–(12.8)	(8.4)
1 (M)	1	26	3 (days)	3.9		
3 (F)	3	33	3	15.0		
			5	14.9		
			12	12.0		
3 (F) av. (on 33 mg.)		33	3–12		12.0–15.0	13.5
3 (F) (on 65 mg.)	2	65†	2–3		13.6–22.8	18.2
	Animals					
Rat, Group d.	8	8	12	2.5		
	4			3.2		
Group d. av.		8	12		2.5–3.2	2.9

* Estimated from PBI.
† Highest tolerated dose.

iodide feeding was dependent upon the level it had reached. The removal of large amounts required several weeks; the drop was about 8 to 10 μg. per 100 ml. during the first week in dogs and rabbits. None remained in the serum by the eighth week in rabbits, dogs and man, regardless of initial concentrations.

3. Minimum Iodide Dosage Eliciting Serum Butanol-Insoluble Iodine

We had previously determined that a dose of 0.4 mg. iodine per kilogram body weight will yield concentrations of 5 μg. per 100 ml. in normal rabbits.[6] The present data (tables 2, 3 and 5) indicated that a dose of 3 mg. iodine per kilogram caused this fraction to appear in dogs; 8 mg. per kilogram were required in rats and 7 to 13 mg. per kilogram were required to have this effect in human beings. Thus, in terms of the iodide dose which elicited a measurable concentration of serum butanol-insoluble iodine, increasing amounts were required, in the indicated order, by normal rabbits, dogs, rats and human beings.

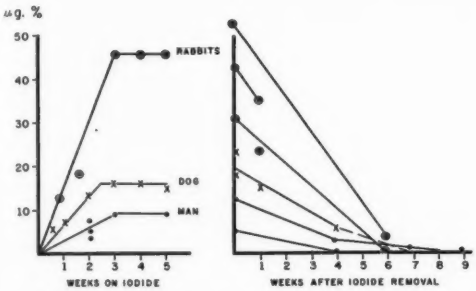

FIG. 1. Development and disappearance of butanol-insoluble iodine. Ordinate represents butanol-insoluble iodine in micrograms per cent; abscissa represent weeks on sodium iodide and after its discontinuance.

TABLE 3.—*Serum Butanol-Insoluble Iodine and Iodide Dosage in Human Beings*

Patient	Dosage mg./Kg.	Time Iodide Fed in Weeks	Butanol-Insoluble Iodine		
			μg.%	Range	Average
"R" (F)	7	1–2	3.6		
		3	2.6		
		4–5	6.8		
		6	4.4		
"R" av.	7	1–6		2.6–6.8	4.3
"G" (M)	13	1–2	2.3		
		7–8	6.3		
1–8 wk av.	13	1–8			4.3
		14	11.7		
		20	12.5		
14–20 wk. av.	13	14–20		11.7–12.5	12.1
"A" (F)	14–24	3	21.5		21.5
"J" (F) "K" (M) "H" (F)	35–40	3	6.0	4.8–7.6	6.0
"C" (F)	35	3	7.4		
		5	6.8		
		6	9.3		
"C" av.	35	3–6		6.8–9.3	7.8
"Z" (F)	37	3	6.4		
		5	10.1		
"Z" av.	37	3–5		6.4–10.1	8.2
"W" (M)	40	3	8.2		
		5	6.8		
		8	5.6		
"W" av.	40	3–8		5.6–8.2	6.7
6 persons average	35–40	3–8		4.8–10.1	6.8

* Patients J, K, H, C, Z and W.

Hypothyroidism, in this respect, increased the efficiency of small doses of iodide. Hypothyroid rabbits fed as little as 0.1 mg. iodide per kilogram exhibited detectable concentrations of serum butanol-insoluble iodine.[6] Similarly, small amounts were produced by this same low iodide dosage in hypothyroid dogs; four times as much was required by hypothyroid rats (tables 4 and 5). These doses were roughly one tenth the amount which had a comparable effect in normal animals. The increased effectiveness of small iodide doses in hypothyroid animals occurred in all species tested; hypothyroid rats required more iodide than rabbits and dogs.

4. Maximum Serum Butanol-Insoluble Iodine Iodine Concentrations

Serum butanol-insoluble iodine increased progressively to 25 μg. per 100 ml. when normal rabbits were fed up to 16 mg. iodide per kilogram daily.[6] In the present experiments (tables 2 and 5) the average level attained on this dosage was 33 μg. per 100 ml.; averages on 32 mg. iodine per kilogram were 48 μg. per 100 ml., and on 188 mg., 33 μg. per 100 ml. The

TABLE 4.—*Serum Butanol-Insoluble Iodine and Potassium Iodine Dosage in Hypothyroid Animals*

Species	No. Detns.	Dosage mg./Kg.	Time Iodide fed in weeks	Butanol-Insoluble Iodine		
				μg.%	Range	Average
Dog 4 (M)	3	0.1	11–19	(6.6)*		
	3		22–31	6.6	4.0–9.5	
5 (M)	1	0.6	3–4	6.0		
6 (M)	1	5.0	3–4	2.3		
Dogs 4, 5, 6 av.		0.1–5.0			2.3–9.5	6.0
Dog 9 (M)	3	21–25	1–10		3.0–6.2	4.1
	3	21–25	13–23		8.3–10.9	9.4
9	3	33–44‡	1–3	7.3	6.0–10.8	
	4	63–74‡	3–6	16.3	15.0–17.5	
	4	83–92‡	7–10	15.9	10.9–21.1	
7 (M)	1	85†	7	(16)*		
8 (M)	1	94†	3–4	13.1		
Dogs 7, 8, 9 av.		63–94	3–8		10.9–21.1	15.8
Rat (*pool of 8*) c.	2	0.4	12		1.5–2.0	1.7
d.	3	4.0	12		7.6–8.9	8.4
e.	3	20	12		9.6–17.1	14.5

* Estimated from PBI.
† Highest tolerated dosage for dogs 7 and 8.
‡ Iodide dosage progressively increased.

TABLE 5.—*Summary of Butanol-Insoluble Iodine in Serum of Various Animal Species*

Dosage I/Kg. (mg.)	Rabbits		Dogs		Rats		Human Beings
	Normal μg. %	Hypothyroid μg. %	Normal μg. %	Hypothyroid μg. %	Normal μg. %	Hypothyroid μg. %	Normal μg. %
Average Values							
<0.1	0	—		0	0	0	0
0.1	0*	4.1*	0	6.6	—	—	—
0.4–0.8	5.3*	20.9*	—	6.0	0	1.7	—
3–5	13.2*	—	(8.4)†	2.3	—	8.4	—
7–8	19.6*	—	—	—	2.9	—	4.3
13	—	—	—	—	—	—	4.3 (12.1)‡
16–22	25.0*	57.3*	—	4.1	—	14.5	—
	32.9	—	—	(9.4)‡	—	—	—
30–40	48.2	—	13.5	7.3	—	—	6.8
63–94	—	—	18.2	15.8	—	—	—
188	32.9	—	—	—	—	—	—
Maximum Values							
	17.0–63.4	43.0–71.0	13.6–22.8	10.9–21.1	—	9.6–17.1	4.8–21.5

* Results reported previously.[6]

† Estimated from serum protein-bound iodine.

‡ After 10 weeks on iodide.

concentrations in individual rabbits varied from 17 to 63 μg. This range of 17 to 63 μg. per 100 ml. presumably represented the maximum concentration of serum butanol-insoluble iodine attainable in rabbits, since dosages of 188 mg. iodine per kilogram elicited no more than did 16 mg. per kilogram.

Dogs exhibited a lesser capacity than rabbits to develop this fraction in their blood, the highest concentration found in the group was 23 μg. per 100 ml., on a dose of 65 mg. iodine per kilogram; the majority of the determinations fell in the range of 12 to 15 μg. per 100 ml. The maximum dose was about as much as could be fed without causing weakness, anorexia and loss of weight.

The maximum concentration of serum butanol-insoluble iodine in human beings fed large doses of iodide was still less than that found in dogs. In six patients treated with 35 to 40 mg. iodine per kilogram for three weeks, it was 6.7 μg. per 100 ml. (4.8 to 8.2). This level was maintained in three who continued on iodide for five to eight weeks, the average in all six patients for the entire period being 6.8 μg. per 100 ml. (4.8 to 10.1). The attainable concentrations of serum butanol-insoluble iodine may vary in some human beings beyond this range. This was shown in patient A who had 21.5 μg. per 100 ml. after three weeks on 14 to 24 mg. iodine per kilogram. Also in patient G, continuing on 13 mg. iodine per kilogram for five months, the serum butanol-insoluble iodine increased in the third month to 12.1 μg. per 100 ml. This was a higher concentration than occurred in patients given more iodide for a shorter period.

Hypothyroid rabbits seemed to produce slightly more serum butanol-insoluble iodine on high iodide dosage than normal rabbits. Concentrations averaging 57 μg. per 100 ml. (43 to 71) were found in hypothyroid rabbits given 16 mg. iodine per kilogram[6] as compared with 37 μg. (17 to 63) occurring in normal rabbits on 16 to 188 mg. iodine per kilogram. On the other hand, hypothyroid dogs attained the same amount of serum butanol-insoluble iodine as normal dogs; 16 μg. per 100 ml. (11 to 21) (table 4) and 18 μg. (14 to 23) (table 2), respectively. Administration of a small iodide dosage for more than three months may increase concentrations progressively. As in patient G, the fraction in hypothyroid dog 9, on 21 mg. per kilogram increased from a mean of 4.1 μg. per 100 ml. in the first 10 weeks, to 9.4 μg. after the thirteenth week.

The highest serum butanol-insoluble iodine found in hypothyroid rats, namely 14.5 μg. per 100 ml. (9.6 to 17.1) was probably submaximal since the maximum iodide dosage fed was only 20 mg. iodine per kilogram (table 4).

Thus, the least iodide dosage which yielded maximum concentrations of this fraction was about 16 mg. per kilogram per day in rabbits, more than 20 mg. in rats, 35 to 40 mg. in man and 63 to 94 mg. per kilogram per day in dogs. Hypothyroidism in rabbits possibly increased the maximum concentration attainable for this species, but did not seem to have a similar effect in dogs.

The same amount of serum butanol-insoluble iodine was formed per milligram of iodine with iodopropylidene glycerol as potassium iodide.

Discussion

In this paper we have defined the amount of iodide ingested daily which results in the appearance of minimum amounts of serum butanol-insoluble iodine, as well as the amount necessary to produce maximum attainable concentrations in various species, both in the normal and in the hypothyroid state. The amount necessary to elicit the appearance of small amounts of this fraction in the serum of rabbits and dogs, is ineffective in rats and man. What is a small dose of iodide in rats and man is a large one for sensitive species such as dogs or rabbits.

The least oral dose which will give rise to a measurable concentration of butanol-insoluble fraction in a species and the amount of iodide required to elicit maximum concentrations run parallel. These levels of dosage may be functions of the relative rates of excretion of inorganic iodine. This is reduced in hypothyroid patients as shown by the lowered renal clearance.[8]

The function of serum butanol-insoluble iodine is not known. It is shown here that its concentration is related to the amount of ingested iodide and is one measure of the organism's response to iodide. Such a measure is useful in evaluating the association of this fraction with serum cholesterol changes in iodide and cholesterol-fed rabbits, in which large amounts of iodide retard and small amounts enhance hypercholesterolemia. The association of this iodine fraction with serum cholesterol in iodide-fed dogs, rats and human beings is under study.

The fact that the maximum levels of serum butanol-insoluble iodine attained in man are not as high as those in other species raises the question whether the patients were given sufficient iodide. They were fed 3 Gm. of potassium iodide daily for three to eight weeks and the maximum levels attained varied from 5 to 22 μg. per 100 ml. The data of Danowski, Johnson and Greenman[9] obtained from patients fed 3 to 7 Gm. of potassium iodide for periods up to six months, indicate a similar range of concentrations as estimated from values of total protein-bound iodine. Such dosages are as much as seem feasible since they are on the margin of inducing iodism. It seems likely that the maximum concentrations attainable in man are lower, and perhaps as individually variable, as in rabbits.

The total serum protein-bound iodine found by Danowski and his associates[10] in two out of six patients on 0.6 Gm. potassium iodide (approximately 7 mg. iodine per kilogram) for four to seven weeks increased slightly, presumably because of formation of the butanol-insoluble fraction. This seems to confirm our own estimate of minimum effective iodide dose in human beings.

Observations with an organic iodine compound, iodopropylidene glycerol, indicate that it is as effective as potassium iodide in increasing the serum butanol-insoluble fraction of protein-bound iodine to a maximum.

Summary

Because of an apparent association between atherogenesis in cholesterol-fed rabbits and the amount of butanol-insoluble protein-bound iodine developing in plasma when iodide is fed, the effect of iodide dosage on this fraction was determined in normal rabbits, in normal and hypothyroid dogs and rats, and in hypertensive patients.

1. Butanol-insoluble iodine makes up most of the increased protein-bound iodine found in the serum of iodide-fed rabbits, dogs, rats and human beings. It appears within a few days after iodide feeding is begun, and dis-

appears four to eight weeks after discontinuing iodide.

2. The oral iodide dosage required to produce measurable concentrations of serum butanol-insoluble iodine was small in rabbits and dogs, larger in rats and man. The daily doses necessary were 0.4 mg. iodine per kilogram for rabbits, less than 3 mg. for dogs, 8 mg. for rats, and 7 to 13 mg. for man.

3. Hypothyroid animals required roughly one-tenth the minimum dosage for normal animals to elicit the same response; namely, 0.1 mg. per kilogram for rabbits and dogs, 0.4 mg. per kilogram for rats.

4. Maximum attainable concentrations appeared in rabbits at an iodide dosage of 16 mg. per kilogram, at more than 20 mg. in rats, at 35 to 40 mg. in man, and at 63 to 94 mg. per kilogram in dogs.

5. Iodopropylidene glycerol was as effective as potassium iodide in producing maximum concentrations of serum butanol-insoluble iodine in rabbits.

Sumario Español

Debido a la aparente asociación entre la aterogénesis en conejos alimentados con colesterol y la cantidad de iodo amarrado a proteina insoluble en butanol que se desarrolla en el plasma cuando se administra ioduro, se determinó el efecto de la dosis de ioduro en esta fracción en conejos normales, en perros y ratas normales e hipotiroides y en pacientes hipertensos.

1. El iodo butanol insoluble compone la mayor parte del incremento en iodo amarrado a proteina que se encuentra en el suero de conejos alimentados con ioduro, perros, ratas y sujetos humanos. Aparece a los pocos dias después de haberse comenzado la administración de ioduro y desaparece de cuatro a ocho semanas luego de haberse descontinuado.

2. La dosis de ioduro oral necesaria para producir concentraciones mensurables de iodo en suero butanol insoluble fué pequeña en los conejos y perros y mayor en las ratas y el hombre. Las dosis diarias necesarias fueron 0.4 mg. de iodo por kilogramo para los conejos, menos de 3 mg. para los perros, 8 mg. para las ratas y de 7 a 13 mg. para el hombre.

3. Animales hipotiroides requirieron toscamente una decima de la dosis minima que se requirio en los animales normales para lograr la misma repuesta; o sea 0.1 mg. por kilogramo para conejos y perros y 0.4 mg. por kilogramo para las ratas.

4. La concentración máxima alcanzable apareció en conejos que se le administraba una dosis de 16 mg. por kilogramo, a más de 20 mg. en las ratas, a 35–40 mg. en el hombre y a 63–94 mg. por kilogramo en el perro.

5. El glicerol de "iodopropylidene" fué tan efectivo como el ioduro de potasio en producir concentraciones máximas de iodo en suero butanol insoluble en conejos.

Acknowledgment

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REFERENCES

[1] Liebig, H.: Die Beeinflussung der experimentellen Atherosklerose durch Jodbehandlung. Arch. exper. Path. u. Pharmakol. **159:** 265, 1931. II. ibid. **175:** 409, 1934.

[2] Turner, K. B.: Studies on the prevention of cholesterol atherosclerosis in rabbits. I. The effect of whole thyroid and potassium iodide. J. Exper. Med. **58:** 115, 1933.

[3] Ungar, H.: Zur Wirkung des Jods auf die Cholesterin-Atheromatose der Kaninchen. Arch. exper. Path. u. Pharmakol. **175:** 536, 1934.

[4] Page, I. H., and Bernhard, W. G.: Cholesterol-induced atherosclerosis. Its prevention in rabbits by the feeding of an organic iodine compound. Arch. Path. **19:** 530, 1935.

[5] Breusch, F., and Thiersch, H.: Der Einfluss des Jods auf die Kaninchen Atheromatose. Ztschr. ges. exper. Med. **95:** 458, 1935.

[6] Brown, H. B., and Page, I. H.: Mechanism of iodide action on cholesterol metabolism. Circulation **5:** 647, 1952.

[7] Rosenthal, S. R.: Studies in atherosclerosis. Chemical, experimental and morphologic. V. Possible dangers in iodine therapy in atherosclerosis of aorta seen from an experimental viewpoint. Arch. Path. **18:** 827, 1934.

[8] Keating, F. R., Jr., and Albert, A.: The metabolism of iodine in man as disclosed with the use of radioiodine (Chap. 15). In Pincus, G.: Recent Progress in Hormone Research. New York, Academic Press, 1949. Vol. 4, p. 429.

[9] Danowski, T. S., Johnson, S. Y., and Greenman, J. H.: Alterations in serum iodine fractions induced by the administration of inorganic iodide in massive dosage. J. Clin. Endocrinol. **10:** 519, 1950.

[10] —, Mateer, F., Weigand, F. A., Peters, J. H., and Greenman, J. H.: Serum iodine fractions in subjects receiving potassium iodide in small dosage. J. Clin. Endocrinol. **10:** 532, 1950.

Prostigmine Inhibition of Ventricular Fibrillation in the Hypothermic Dog

By A. V. Montgomery, Ph.D., Arthur E. Prevedel, M.D., and Henry Swan, M.D.

This study shows that when prostigmine is given via coronary perfusion in the hypothermic dog, cardiac surgery can be performed without ventricular fibrillation resulting. This action of prostigmine seems to be due to an accumulation of acetylcholine, since prostigmine's antifibrillatory action can be reproduced by a continuous coronary perfusion of acetylcholine or by stimulation of the vagus nerve. A possible relationship between potassium and ventricular fibrillation is discussed.

BIGELOW and co-workers[1] have shown that the metabolic rate of dogs whose body temperature has been cooled to 20 C. rectal temperature is only about 15 per cent of control. This circumstance moved Bigelow and other coworkers[2] to deliberately occlude circulation for periods of 15 minutes without observable damage to the heart or central nervous system in the surviving animals. However, about half of his animals died of ventricular fibrillation during the experiment.

Several workers[3,4,5] have attested to the increased irritability of the ventricles in the hypothermic dog, but to date the explanation for this observation has been elusive. It appears clear that cardiac hypoxia, when the circulation is intact in the dog at 20 C. or above, does not seem to be a najor factor. Penrod[6] has shown that the arteriovenous oxygen difference across the coronary circulation remains normal until the rectal temperature falls below 20 C. Lower temperatures resulted in a rapid decrease in the A-V oxygen difference. This observation has been confirmed and extended recently by Edwards and associates.[7]

In a search for other factors which might contribute to the increased irritability of hypothermia, Swan and some of his colleagues[8] studied the plasma and thiocyanate volumes, blood pH, and sodium, potassium and chloride of the plasma in the normothermic hyperventilated animal and in the hypothermic animal under the influence of both hyperventilation and hypoventilation. They also reported that when animals were cooled to a rectal temperature of 25 C. and inflow occlusion to the heart was instituted, many animals incurred ventricular fibrillation, especially upon the release of the occlusion. However, the incidence of fibrillation was a function of ventilatory rate: in the hypoventilated group it was 50 per cent; in the hyperventilated group, 8 per cent.

The only recognized difference in the composition of the blood between these two groups was the pH. In both groups the plasma potassium was consistently low; it was felt likely, however, that intracellular differences might exist, and that an inverse relation between hydrogen ion concentrati n and intracellular potassium in the hypothermic dog might be present. Although it was found that in the hyperventilated hypothermic animal the loss of extracellular potassium was not accounted for by renal excretion of the ion, the difference was quantitatively small. This was interpreted to mean that either intracellular potassium remained the same or was increased slightly. Subsequently, somewhat more convincing evidence was obtained in the opposite direction in hypoventilated animals. Unpublished observations from this laboratory show that in the hypoventilated hypothermic dog

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the renal excretion of potassium is several times greater than would be required to account for the loss of extracellular potassium. It is felt that this observation indicates a loss of intracellular potassium in the hypothermic animal with a low blood pH.

There is another apparent relationship between fibrillation and potassium. Swan and associates[8] found that the fibrillating hypothermic heart could rarely be converted to a normal rhythm by massage and electric shock. However, when the coronary arteries of the fibrillating heart were perfused with a potassium chloride solution (1 mEq. per milliliter) the fibrillation could usually be converted directly or by use of electric shock.

The above observations seemed to fit into a general theory previously advanced by Hooker.[9] He had found that ventricular fibrillation in the isolated perfused heart could be converted by the addition of potassium to the perfusion medium. He also found that during ventricular fibrillation the heart lost potassium to the perfusion medium. From these observations he suggested that the potassium added to the perfusion fluid caused, by chemical mass action, the fibrillating myocardium to make up its potassium deficiency and by so doing restored normal ventricular rhythm.

The above observations led us to explore the effect of certain agents known to have an effect on potassium distribution. Grieg and coworkers[10] have described such an effect of acetylcholine on the isolated guinea pig heart. Unpublished observations by Holmes and Montgomery[11] have shown that potassium movement between the intracellular and extracellular spaces can be affected by acetylcholine and cholinesterase inhibitors. The current report describes certain observations on the effect of prostigmine, acetylcholine, and stimulation of the vagus nerve on ventricular fibrillation in the hypothermic dog.

Methods

Two groups of experiments are presented: those concerned with the effect of certain drugs or procedures on ventricular fibrillation in hypothermia, and those concerned with the arteriovenous potassium difference across the coronary circulation during ventricular fibrillation or various degrees of ventilation during hypothermia. In the first group, two types of stimuli were used for the induction of ventricular fibrillation: ventricular incision and catheterization of the coronary sinus during inflow and outflow occlusion of the heart in the dog at 25 C. rectal temperature. The influence of prostigmine, acetylcholine, and vagal stimulation on the effect of these stimuli was studied.

In the initial experiments prostigmine methylsulfate (0.05 ml. per kilogram of a 1:4000 solution) was given intravenously five minutes before circulation was occluded and ventriculotomy performed. Later prostigmine was administered by a technic which we have termed coronary perfusion. This mode of administration was as follows. The azygos vein was ligated and the superior and inferior venae cavae occluded. The ascending aorta was occluded by a Potts clamp. The outflow occlusion was applied about 15 seconds after the inflow to prevent acute dilatation of the heart. Then prostigmine (1:4000) was injected into the aorta proximally to the clamp so that as the heart contracted the drug was perfused through the coronary circulation. If the drug was used only after fibrillation had ensued, cardiac massage was instituted to force the drug through the coronaries. When acetylcholine was used, its short action required continuous administration throughout the period of cardiac manipulation and release of occlusion. Both drugs were administered slowly until the heart rate was reduced to between 10 to 25 beats per minute. An initial 1 ml. injection of prostigmine was given and the heart rate was determined. Prostigmine was then given, 0.5 ml. at a time, until the desired rate was achieved. Acetylcholine was administered at a rate of 0.5 mg. per minute until the desired rate was achieved, then it was given more slowly throughout the procedure in quantities just sufficient to maintain the heart rate between 10 to 25 beats per minute. When vagal stimulation was being used to increase the threshold to ventricular fibrillation, the right vagus nerve was stimulated with a square wave of voltage varying from 25 to 40 volts and at a frequency of from 8 to 25 stimuli per second. These variables were adjusted to give the same heart rate that was obtained in the prostigmine and acetylcholine experiments. Usually the frequency of stimulation had to be gradually increased during the procedure in order to maintain this slow rate.

All animals were anesthetized with 35 mg. per kilogram of sodium pentobarbital given intravenously before immersion in an ice bath. More pentobarbital was administered if any observable shivering occurred. When the animal was placed in the ice, it was connected to a respirator supplied with pure oxygen.

Cannulation of the coronary sinus was accomplished in the following manner. A small transverse skin incision was made to expose the external jugular

vein. A no. 18 polyethylene catheter with a small curved glass tip was placed into the vein and pushed into the superior vena cava. When vagal stimulation was to be performed, the right or both vagus nerves were isolated. A right thoracotomy was made through the fifth intercostal space and upon opening the chest the azygos vein was ligated. Both cavae were isolated and the pericardial sac opened. Both cavae were then occluded with umbilical tape and 15 seconds later the ascending aorta was occluded just distal to the ostia of the coronary arteries. The right atrium was then opened widely and the catheter tip was inserted into the coronary sinus. A suture into the posterior wall of the atrium held the catheter tip in place. The atrium was filled with saline and the opening and the incision closed with a curved Potts clamp. The aortic occlusion was released first, followed by simultaneous release of both cavae. The total occlusion time was from three to four minutes. If vagal stimulation was being used to prevent fibrillation during the procedure, the nerve was stimulated until after the atrium had been closed with a continuous mattress stitch.

Blood samples were drawn periodically from the coronary sinus and from the femoral artery. These samples were analyzed for potassium by a Janke flame photometer.

Results

Table 1 reveals data obtained from experiments on 65 dogs. All of these animals were hyperventilated with oxygen and were cooled to 25 C. The stimulus for ventricular fibrillation was a 3 to 4 cm. incision into the right ventricle. It is seen that in the control series of animals without pretreatment 23 out of 23 animals incurred ventricular fibrillation following ventriculotomy.

Prostigmine 1:4000 (0.05 cc. per kilogram) was administered intravenously five minutes before circulatory arrest to 15 animals. Only seven, or about 50 per cent, of these animals developed ventricular fibrillation following ventriculotomy. The remaining eight animals are still living. Five of the animals that fibrillated were converted to a normal sinus rhythm by cardiac massage and electric shock. All of the converted animals also survived the entire procedure.

The next experiments concerning the effect of prostigmine had a dual purpose. The first was of a practical nature. We wanted to see if a higher concentration of prostigmine locally to the heart might decrease the incidence of ventricular fibrillation without the total dose administered being in the lethal range of prostigmine. The second purpose was to determine whether the antifibrillatory effect was a local one rather than a general systemic effect.

Table 1.—*Ventricular Fibrillation in Hypothermic Dogs Using Ventriculotomy as Stimulus*

	No. of Dogs	Ventric. Fibrill.	Resuscitation
Control	23	23	0 of 23 attempts
Prostigmine in open circulation	15	7	5 of 5 attempts
Prostigmine by coronary perfusion	16	0	—
Acetylcholine by coronary perfusion	5	0	—
Continuous stimulation of right vagus	6	2	2 of 2 attempts

With these ideas in mind, 1 to 3 ml. of 1:4000 solution of prostigmine was administered by coronary perfusion as described above. The clearly visible effects of prostigmine administered in this manner are quite dramatic. Even though inflow to the heart is occluded, the myocardium becomes pink, the diastolic volume is reduced, and the contractions become more forceful. Table 1 shows that of the 16 animals treated in this manner ventriculotomy failed to induce ventricular fibrillation in a single instance. In addition to the routine right ventriculotomy, eight of these animals survived a left ventriculotomy and the creation of an interventricular septal defect all in the same operative procedure. All of these animals warmed at the normal rate and lived until sacrificed weeks later.

Since the cholinesterase enzyme normally hydrolyzes acetylcholine, the effects of cholinesterase inhibitors can often be explained on the basis of an accumulation of acetylcholine. If such is the mode of action of the antifibrillatory effect of prostigmine, one would expect a continuous perfusion of acetylcholine through the coronaries to duplicate the effect. Table 1 shows that in five animals given such perfusion, acetylcholine did prevent ventricular fibrillation following ventriculotomy.

Since the vagus nerve is thought to influence

TABLE 2.—*Ventricular Fibrillation in Hypothermic Dogs Using Coronary Sinus Catheterization as Stimulus*

	No. of Dogs	Ventric. Fibrill.	Resuscitation (with Prostigmine
Control	12	11	11
Prostigmine by coronary perfusion	21	0	—
Continuous stimulation of right vagus	10	0	—

the heart by the release of acetylcholine, one would expect that stimulation of the peripheral stump of the vagus would mimic the antifibrillatory effect of prostigmine and acetylcholine. In six experiments, such vagal stimulation protected four animals from fibrillation, while the remaining two were easily converted to normal rhythm by massage and electric shock.

It was desired to catheterize the coronary sinus in order to determine coronary sinus potassium concentration. In the cold dog this was found to be a potent stimulus to fibrillation. Table 2 shows that 11 out of 12 dogs developed fibrillation with the catheterization procedure. None of these animals could be converted to a normal rhythm by cardiac massage and electric shock. However, after coronary perfusion of prostigmine all 11 animals were readily converted by electric shock. This table also shows that coronary perfusion of prostigmine prior to catheterization protected another 21 dogs against ventricular fibrillation. Table 2 also reveals that stimulation of the vagus nerve during the catheterization protected all 10 against fibrillation.

On the basis of observations previously reported,[7] it was suspected that blood pH influenced the concentration of potassium in the myocardium. Since it was shown[7] that hyperventilation reduces the incidence of ventricular fibrillation in the hypothermic dog as compared with the hypoventilated animal, the effect of pH on potassium metabolism of the heart receives greater importance. In order to shed light on this point we examined the arteriovenous difference in plasma potassium concentration across the coronary circulation in the hypothermic dog during hypoventilation and hyperventilation. Such data should indicate whether the myocardium is gaining or losing the ion. The results of these experiments are presented graphically in figure 1. In this figure, the points joined by the solid lines are the mean A-V differences in four dogs; the dotted lines represent the extremes. A positive difference (A greater than V) indicates that the heart is taking up potassium, while a negative difference (V greater than A) indicates that the heart is losing potassium. These data clearly demonstrate that, regardless of whether the animal is started on hyperventilation and switched to hypoventilation, or vice versa, when the animal is hypoventilated (low pH) the heart is taking up potassium; whereas, when the animal is hyperventilated (high pH) the heart achieves or maintains potassium balance, neither gaining nor losing significant amounts.

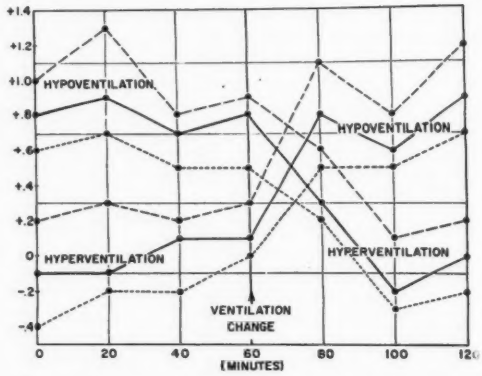

FIG. 1. Arteriovenous difference in plasma potassium concentration across the hypothermic myocardium, 25 C. during variations in blood pH controlled by respiration. (Simultaneous femoral artery and coronary sinus blood samples.)

Since Hooker[8] has shown that during ventricular fibrillation the isolated perfused heart loses potassium, we wondered if the same conditions pertained in the cold intact heart. Any time that ventricular fibrillation occurred when the coronary sinus catheter was in place, sinus samples were drawn as soon as possible. The stimuli for fibrillation in this group of animals varied widely. The results of this heterogenous group of experiments are reported

TABLE 3.—*Serum Potassium Level of Coronary Sinus Blood before and during Ventricular Fibrillation*

Dog No.	Before Fibrillation (mEq./L.)	During Fibrillation (mEq./L.)
F-1	2.56	7.42
F-2	3.02	8.59
F-3	2.67	5.64
F-4	3.13	9.69
F-5	2.01	6.15
F-6	2.15	8.30
F-7	2.68	7.53
Mean.....	2.17	7.61

in table 3. The mean coronary sinus potassium before fibrillation was 2.6 mEq. per liter and 7.5 mEq. per liter during fibrillation. In every animal more potassium was leaving the heart during fibrillation than before.

DISCUSSION

The results reported here show that the administration of prostigmine to the hypothermic dog has a pronounced antifibrillatory effect. When this drug is given by coronary perfusion, it is more effective. Since prostigmine is a cholinesterase inhibitor, one might expect that the antifibrillatory effect of prostigmine is secondary to an accumulation of acetylcholine. Evidence for this idea receives support from two other observations in the present report. Infusion of acetylcholine through the coronaries inhibits ventricular fibrillation, as does also an increase in endogenous acetylcholine by vagal stimulation. Prostigmine appears to be the drug of choice for practical application. The use of this agent gives promise of being a potent weapon for the prevention and management of the ventricular fibrillation associated with hypothermia. In our hospital we are now giving this drug clinical trial.

In the present state of knowledge, it is impossible to describe the underlying phenomena at the cellular level which influence ventricular fibrillation or to portray the mechanism by which acetylcholine prevents fibrillation in the hypothermic dog. However, there is a growing body of evidence which strongly implicates potassium distribution as being related to this phenomenon. Howell[12] showed long ago that stimulation of the vagus nerve caused a loss of potassium from the heart. Hooker[9] has shown that during ventricular fibrillation the isolated perfused heart is losing potassium. The results presented here show that the same can be said of ventricular fibrillation in the hypothermic dog. Bigelow[1] reported a 50 per cent incidence of ventricular fibrillation following release of a 15 minute inflow occlusion in the hypothermic dog. The pH of his animals was low because they were breathing a gas containing a high concentration of carbon dioxide. Swan and associates[8] reported the same incidence of ventricular fibrillation when the pH was depressed by hypoventilation of the animal. However, the incidence of fibrillation was reduced to 8 per cent when the animals were hyperventilated. The results reported here suggest that the high incidence of fibrillation associated with hypoventilation in hypothermia occurs under the conditions of a myocardium which has gained potassium. In short it appears that an acidotic, hypothermic myocardium gains potassium and is subject to fibrillation; but whenever the myocardium, warm or cold, acidotic or alkalotic, enters fibrillation, potassium is released from the heart.

Another suggestive line of investigation relating potassium to fibrillation was begun by Brown and Miller[13] who found a high incidence of fibrillation in dogs suddenly changed from a breathing mixture containing a high concentration of carbon dioxide to room air. Young, Sealy, and Harris[14] have recently focused attention on the changes occurring during the first few minutes of normal respiration in similar experiments. They found that the serum potassium rose as the pH fell when the animals were being ventilated with 20 per cent carbon dioxide. After the animals had been breathing this gas mixture for two to four hours, they were suddenly allowed to breath air. He found that this maneuver resulted in a rapid rise in pH, but, more importantly, the serum potassium at first rose abruptly to even higher levels during the first few minutes before beginning a fall toward normal. His animals incurred ventricular fibrillation during the time of the abrupt rise

in serum potassium. Intravenous injection of 3 per cent sodium chloride solution reduced the potassium rise and prevented ventricular fibrillation. The cause of the temporary but severe dissociation of potassium and pH during these first few minutes is unknown.

Grieg and associates[10] have made observations on the rate of movement of potassium across the myocardial membrane of the guinea pig. They have reported that acetylcholine increases the rate of movement of potassium across cell membranes, the direction of movement depending on the direction of deviation from the normal potassium gradient across the membrane. On the basis of these observations, one would predict that if serum potassium were suddenly lowered, thus increasing the gradient, potassium would tend to move out of the cell. Acetylcholine would accelerate the shift. This relationship has not been demonstrated in the cold animal.

The varied data presented above certainly do not allow a definitive description of the relation between potassium distribution and ventricular fibrillation. However, taken as a whole they strongly suggest that such a relationship exists. Much further work needs to be done in this area of investigation.

At the integrative level, however (that is, in the area of mechanisms impinging on and regulating cell activity), at least one working hypothesis can be presented. It is our intention to submit this hypothesis to experimental evaluation in the immediate future. Adrenaline and probably sympathetic impulses to the heart may induce ventricular fibrillation or potentiate other factors which induce fibrillation. There is evidence in the literature which indicates that under hypothermia the heart is receiving predominantly sympathetic impulses. Bigelow[2] has estimated the peripheral resistance in hypothermic animals by the simultaneous determination of arterial pressure and cardiac output. This observation suggests a strong sympathetic activity. In the experiments reported here concerning vagal stimulation, it was observed that section of the vagus nerves does not lead to a cardiac acceleration. This finding confirms a similar observation by Cookson and DiPalma.[15] This could mean either that in hypothermia there is an absence of vagal cardiac impulses or that the heart is no longer sensitive to acetylcholine released at the vagal endings. Two observations militate against the latter view: electrical stimulation of the peripheral vagus and acetylcholine perfusion cause cardiac slowing in the cold heart.

The above considerations lead us to suggest the following possible mechanism. The low systemic arterial pressure in hypothermia activates the carotid sinus reflex, resulting in a lack of vagal impulses to the heart, an increase in sympathetic impulses to the heart, and an intense vasoconstriction mediated by sympathetic fibers. From this point of view the antifibrillatory effects of prostigmine, acetylcholine and vagal stimulation become more meaningful. Each procedure increases a depressed parasympathetic influence on the cold heart, thus restoring a more nearly normal balance of sympathetic and parasympathetic effects.

Summary

1. Prostigmine has a marked antifibrillatory effect upon the ventricular myocardium of the hypothermic dog.

2. Acetylcholine or vagus nerve stimulation also has this effect.

3. The hypothermic myocardium during respiratory acidosis gains potassium.

4. The hypothermic myocardium during respiratory alkalosis maintains potassium balance.

5. The hypothermic myocardium in ventricular fibrillation loses potassium.

Sumario Español

1. La prostigmina tiene un efecto antifibrilatorio marcado en el miocardio ventricular del perro hipotérmico.

2. La acetilcolina o la estimulación del vago también tienen este efecto.

3. El miocardio hipotérmico gana potasio durante la acidosis respiratoria.

4. El miocardio hipotérmico mantiene el balance de potasio durante la alcalosis respiratoria.

5. El miocardio hipotérmico pierde potasio durante la fibrilación ventricular.

REFERENCES

[1] Bigelow, W. G., Lindsay, W. K., Harrison, R. C., and Lindsay, W. K.: Oxygen transport and utilization in dogs at low body temperatures. Am. J. Physiol. **160:** 125, 1950.

[2] —, Callaghan, J. C., and Hopps, J. A.: General hypothermia for experimental intracardiac surgery. Ann. Surg. **132:** 531, 1950.

[3] Hegnauer, A. H., D'Amato, H. D., and Flynn, J.: Influence of intraventricular catheters on the course of immersion hypothermia in the dog. Am. J. Physiol. **167:** 63, 1951.

[4] Hoff, H. E., and Stansfield, H.: Ventricular fibrillation induced by cold. Am. Heart J. **38:** 193, 1949.

[5] Bigelow, W. G., Lindsay, W. K., and Greenwood, W. F.: Hypothermia. Its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. Ann. Surg. **132:** 849, 1950.

[6] Penrod, K. E.: Cardiac oxygenation during severe hypothermia in the dog. Am. J. Physiol. **164:** 79, 1951.

[7] Edwards, W. S., Tuluy, S., Reber, W. E., Siegel, A., and Bing, R. J.: Coronary blood flow and myocardial metabolism in hypothermia. Ann. Surg. **139:** 275, 1954.

[8] Swan, H., Zeavin, I., Holmes, J. H., and Montgomery, V.: Cessation of circulation in general hypothermia. I. Physiologic changes and their control. Ann. Surg. **138:** 360, 1953.

[9] Kehar, N. D., and Hooker, D. R.: Evidences of an altered tissue state in ventricular fibrillation. Am. J. Physiol. **112:** 301, 1935.

[10] Holland, W. C., Dunn, C. E., and Grieg, M. E.: Studies on permeability. VIII. Role of acetylcholine metabolism in the genesis of the electrocardiogram. Am. J. Physiol. **170:** 339, 1952.

[11] Holmes, J. H., and Montgomery, A. V.: Unpublished observations.

[12] Howell, W. H.: Vagus inhibition of the heart in its relation to the inorganic salts of the blood. Am. J. Physiol. **15:** 280, 1906.

[13] Brown, E. B., and Miller, F.: Ventricular fibrillation following a rapid fall in alveolar carbon dioxide concentration. Am. J. Physiol. **169:** 56, 1952.

[14] Young, G. W., Sealy, W. C., Harris, J., and Botwin, A.: The effect of hypercapnea and hypoxia on the response of the heart to vagal stimulation. Surg., Gynec. and Obst. **93:** 51, 1951.

[15] Cookson, B. A., and DiPalma, J.: Effect of vagal section and quaternary ammonium compounds on bradycardia of severe hypothermia. Federation Proc. **13:** 344, 1954.

The Spatial Vectorcardiogram in Left Ventricular Hypertrophy

By L. G. Horan, M.D., G. E. Burch, M.D., J. A. Abildskov, M.D., and J. A. Cronvich, M.S.

A study of 90 patients with left ventricular hypertrophy revealed a typical configuration of the spatial vectorcardiogram in most of the subjects. Typically the QRS sÊ-loop was smooth, wide and rounded, inscribed in a counterclockwise direction and placed largely to the left and above the isoelectric point in its frontal plane projection. The left sagittal plane projection of the QRS sÊ-loop was long, narrow and directed largely upward and posteriorly. The typical T sÊ-loop was small, smooth, horseshoe-shaped and counterclockwise in inscription in both frontal and left sagittal plane projections. In some instances the QRS sÊ-loop was similar to that of the normal but was always accompanied by an abnormal T sÊ-loop.

THE electrocardiographic features of left ventricular hypertrophy are frequently not clearly separable from those produced by cardiac position and by abnormalities of the myocardium other than hypertrophy. On the other hand, subjects demonstrated to have left ventricular hypertrophy by other methods of examination may have a normal electrocardiographic configuration of the QRS complex with or without T-wave abnormalities. The following study was undertaken to provide a description of the spatial vectorcardiogram in left ventricular hypertrophy recorded with the equilateral tetrahedron reference system and to investigate its possible role in making these distinctions. Others have studied left ventricular hypertrophy with other reference frames.[1-5]

Materials and Methods

The 90 patients with left ventricular hypertrophy studied ranged in age from 27 to 80 years, and 70 were male and 20 female. Evidence for left ventricular hypertrophy was essentially indirect since only five cases have been followed to autopsy thus far (table 1). Cases were selected on the basis of clinical, roentgenographic and electrocardiographic study from patients with diseases which commonly result in left ventricular hypertrophy. Spatial vectorcardiograms were recorded, using the equilateral tetrahedral reference system and cathode ray oscilloscopes. Projections on the frontal, right, left and superior planes were each photographed simultaneously with a projection on the plane sagittal to each as viewed from the subject's left. Stereoscopic views of the frontal, left, right and superior planes were also recorded. Records were also obtained with the amplification increased to obtain adequate delineation of the T sÊ-loop and junction J from the isoelectric point.

The standard leads, V_1 through V_6, unipolar limb leads and a unipolar lead from the back and bipolar leads from the back electrode and each of the other electrode positions defining the equilateral tetrahedron were recorded shortly after the vectorcardiograms. Proper pairs of leads were recorded simultaneously, so that any portion of any lead could be temporally oriented with respect to any other lead. Details of the methods of recording have been published previously.[6]

The vectorcardiograms were analyzed to determine the location of approximate areas of the QRS and T sÊ-loops in the frontal and left sagittal planes, the contour and direction of inscription of these loops and the spatial relationship of junction J to the isoelectric point. Measurements were made of the length and direction of the maximal mean instantaneous vectors of the QRS and T sÊ-loops in the frontal and left sagittal projections and of the maximal extent of the QRS sÊ-loop posterior to the isoelectric point. Not all of the tracings were suitable for measurement of the T sÊ-loop and the J displacement.

Results

QRS sÊ-loop. The typical QRS sÊ-loop was smooth, wide and was inscribed in a counterclockwise direction in the frontal plane projection. Two otherwise typical records in which

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the QRS sÊ-loops were inscribed in a clockwise direction have been included in this group. In 19 records the frontal plane projection of the QRS sÊ-loop was elliptoid in contour (fig. 1*a*) while in 21 records the frontal plane projection was roughly circular in form (fig. 1*b*). The enclosed area was largely located in the first sextant of a triaxial reference frame applied to that plane. The left sagittal projection was usually either thin and line-like or a long, narrow, figure-of-eight shaped loop with the maximal instantaneous vector oriented near the −60 degree axis of a triaxial reference system applied to that plane with its ±180 degree axis located anteriorly. Fifty-three (59 per cent) of the 90 subjects had spatial vectorcardiograms of this typical group, including

TABLE 1.—*Autopsied Cases*

Sex	Age (yrs.)	QRS sÊ-loop	Etiology of Heart Disease	Heart Wt. (Gm.)	Ventricular Thickness (cm.)	
					Left	Right
F	38	Type 1	HCVD with Cong. HF	600	1.8	0.5
M	51	Atypical	HCVD with moderate Cong. HF	640	3.1	0.7
M	66	Atypical	ASHD and HCVD	820	2.4	0.4
M	71	Type 1	ASHD and HCVD	600	2.0	0.7
M	69	Typical	Syph. HD	650	2.5	1.0

HCVD, hypertensive cardiovascular disease; Cong. HF, congestive heart failure; ASHD, arteriosclerotic heart disease; Syph. HD, syphilitic heart disease.

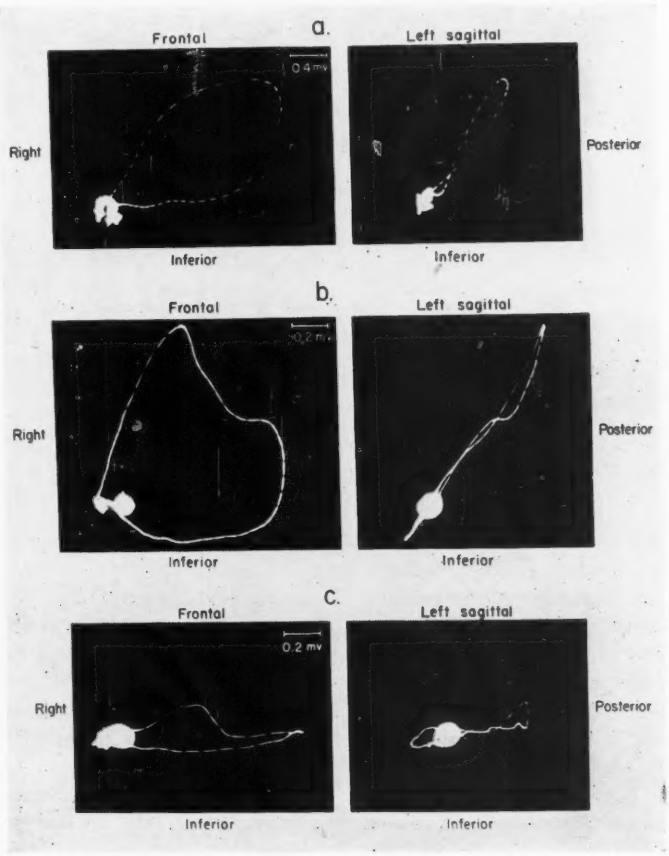

FIG. 1. Frontal and left sagittal plane projections of typical spatial vectorcardiograms observed in left ventricular hypertrophy. In the frontal plane projection many of the QRS sÊ-loops had an elliptoid contour (*a*) but almost as many had a circular contour (*b*). Many of the QRS sÊ-loops were directed posteriorly and to the left (*c*). The typical horseshoe-shaped T sÊ-loop is evident.

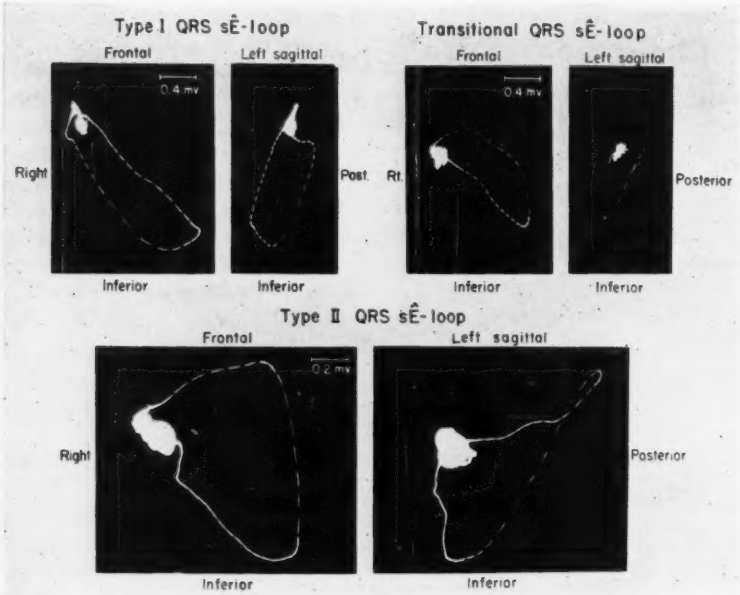

FIG. 2. Examples of spatial vectorcardiograms showing configurations of the QRS sÊ-loop resembling the three types previously described for normal subjects.[2]

TABLE 2.—*Maximal Vectors*

	QRS Frontal		QRS Sagittal		T Frontal		T Sagittal		J Frontal		J Sagittal		Posterior Extent
	mv	angle	mv	angle	mv	angle	mv	angle	mv	angle	mv	angle	mv
Number of subjects	87	90	87	90	52	54	48	49	54	56	44	45	85
Maximal	2.30	+123°	2.26	+164°	0.38	+16°	0.45	+105°	0.26	+63°	0.27	+56°	1.80
Minimal	0.27	−90°	0.29	−63°	0.05	−53°	0.05	−16°	0.02	−78°	0.02	−34°	0.00
Average	0.95	−1°	0.82	+5°	0.16	+177°	0.16	−151°	0.11	−168°	0.10	−145°	0.56
	See figure 4				See figure 6				See figure 5				

minor variations attributable to slight rotation of the loop about vertical, transverse or anteroposterior axes through the isoelectric point. In 13 of these subjects the QRS sÊ-loop appeared to have been rotated backward about the transverse axis, so that it lay almost in a horizontal plane through the isoelectric point thus being largely directed posteriorly and to the left (fig. 1*c*).

Twenty-eight QRS sÊ-loops appeared very similar in configuration and orientation to the QRS sÊ-loops in normal subjects and were subdivided into those which resembled normal types 1 and 2 and transitional patterns as previously described (fig. 2).[7] However, nine of these loops showed a rotation of the distal tip of the loop which will be discussed later (fig. 3). There remained nine QRS sÊ-loops which could not be classified as typical either of left ventricular hypertrophy or of normal appearance.

Fourteen of the 19 instances of clockwise inscription in the frontal plane projections were found among the 28 QRS sÊ-loops of normal appearance and 10 of these resembled the normal type 1 pattern (table 3). The inscription of the QRS sÊ-loop was counterclockwise in the frontal projection in 69 pa-

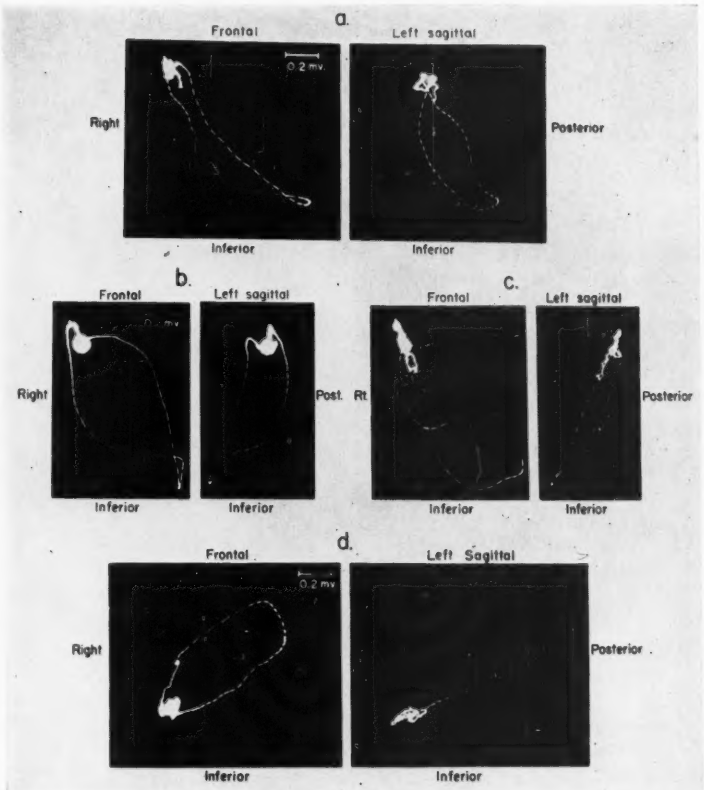

FIG. 3. Examples of the spatial vectorcardiograms obtained from patients with left ventricular hypertrophy. Records *a* and *b* show slight rotation of the distal tip of the QRS sÊ-loop. Record *c* shows more marked rotation of the distal portion so that the major area of the frontal plane projection of the QRS sÊ-loop is enclosed by a counterclockwise inscription. Record *d* is a typical spatial vectorcardiogram of left ventricular hypertrophy. These spatial vectorcardiograms (*a*, *b* and *c*) may represent progressive variations in amount of rotation of the QRS sÊ-loop toward the ultimate development of the more typical pattern (*d*) of left ventricular hypertrophy.

TABLE 3.—*QRS sÊ Configurations of Spatial Vectorcardiograms of 90 Patients with Left Ventricular Hypertrophy*

Configuration	Number Having		
	Clockwise inscription in frontal plane	Counterclockwise inscription in frontal plane	Spatial rotation of distal tip
Typical LVH (53 patients)	2	51	0
Similar to normal			
a. Type 1 (12 patients)	10	2	8
b. Transitional (4 patients)	2	2	1
c. Type 2 (12 patients)	2	10	0
Abnormal but not typical LVH (9 patients)	3	6	0
Total	19	71	9

tients and in the left sagittal projection in 66 patients. The trace of all of the QRS sÊ-loops, except two, was inscribed in a counterclockwise direction in the superior projection.

The maximal instantaneous axes in frontal and left sagittal planes of all the QRS sÊ-loops are shown in figure 4, and the average and extreme values in table 2.

Junction J. Junction J characteristically lay to the right of and anterior to the isoelectric point. The variations may be seen in figure 5. There was no apparent constant relationship between the form of the QRS or T sÊ-loops and the position of junction J.

T sÊ-loop. The typical T sÊ-loop was found to be small compared to the normal T sÊ-loop.[2]

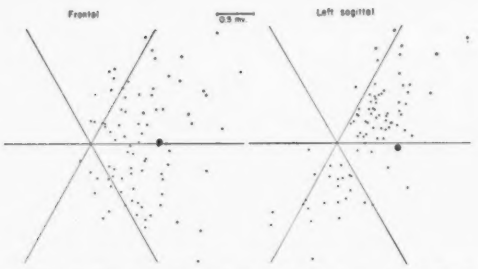

FIG. 4. Magnitude and direction of maximal QRS sÊ vectors in left ventricular hypertrophy in frontal and left sagittal planes.

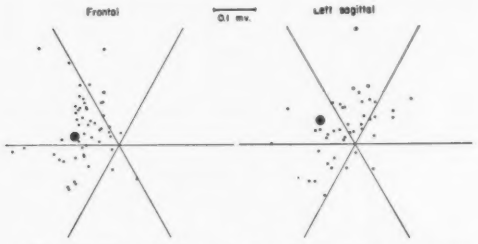

FIG. 5. Magnitude and direction of displacement of junction J in left ventricular hypertrophy in frontal and left sagittal planes.

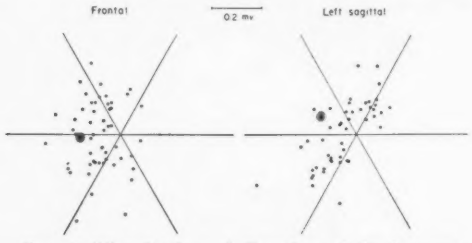

FIG. 6. Magnitude and direction of displacement of maximal T sÊ vectors in left ventricular hypertrophy in frontal and left sagittal planes.

It was smooth, horseshoe-shaped and inscribed in a counterclockwise direction in both frontal and left sagittal projections. It was located in the third and fourth sextants of the triaxial reference system in the frontal plane and in the second, third and fourth sextants in the left sagittal plane. The variations in the maximal instantaneous axes of the T sÊ-loops are shown in figure 6 and table 2.

DISCUSSION

An attempt to explain the shape of the QRS sÊ-loop typically found in left ventricular hypertrophy may begin with consideration of the direct effect of increased left ventricular muscle mass on the mean instantaneous pathway of depolarization. The finding of a QRS sÊ-loop which is traced first slightly downward and forward and which ultimately completes a wide elliptoid configuration directed leftward, upward and posteriorly is in accord with the conventional concept that the intensity and duration of the process of depolarization is, within limits, proportional to the thickness of the muscle mass through which it moves. Contributing to this configuration may be an indirect effect of increased left ventricular mass, namely, rotation of the heart which is usually in a counterclockwise direction as viewed from the apex.

The positions of the heart within the chest with its variations during cardiac and respiratory cycles, variations in electrical conductivity of the extracardiac tissues and other factors were probably responsible for the deceptively wide variations in the configurations of the plane projections of the QRS sÊ-loop as well as the other components of the spatial vectorcardiograms. Careful examination revealed that many of the differences were only apparent and were in fact the result of visualizing single plane projections thus re-emphasizing the necessity to observe the vectorcardiogram in three dimensions.

There are several possibilities to be considered as to the underlying mechanisms producing displacement of junction J to the right of and anterior to the isopotential point in left ventricular hypertrophy: (1) prolonged depolarization; (2) early but normal repolarization; (3) early but abnormal repolarization and (4) any combination of these factors. Examination of the electrocardiograms of patients with left ventricular hypertrophy reveals that the downstroke of the R passes through the baseline en route to J, but inspection of the spatial vectorcardiogram readily demonstrates that the last portion of the QRS does not pass through the isoelectric point in space. Because the QRS sÊ-loop usually arrives at neither J nor the isoelectric point within 0.08 second, it is evident that depolarization is longer than usual and that early repolarization (either

normal or abnormal) is not the only factor involved in the spatial displacement of J. Although the reasons for the anterior and dextral displacement of junction J are not known and although the initial forces of repolarization may form the major contribution, certain regions of late depolarization may possibly contribute to this displacement including (1) the posterobasal portion of the left ventricle, (2) the adjacent basal portion of the septum (from left to right) and (3) the pulmonary conus area.

The causes of the abnormal size, shape and orientation of the T sÊ-loop in left ventricular hypertrophy are conjectural. J displacement produced an open T sÊ-loop. The greater overlap of depolarization and repolarization may possibly account for some of its reduction in size as compared with that of the normal. In general, the T sÊ-loops and QRS sÊ-loops were oriented in opposite directions. This most likely represents a change in the order of repolarization from the normal.

Examination of the 28 records with normal appearing QRS sÊ-loops disclosed several interesting facts. First, this group accounted for 14 of the 19 instances of clockwise inscription of the QRS sÊ-loop in its frontal plane projection. Ten of these with clockwise inscriptions were of the type 1 normal configuration but 8 of these 10 (as well as one of the two clockwise transitional loops) showed a slight uptwist of the distal tip of the otherwise normally-directed QRS sÊ-loop. It is possible that this may be one of the earliest indications of left ventricular hypertrophy noted in the vectorcardiogram and suggests the manner of change from the usual normal clockwise rotation of the loops to the typical counterclockwise rotation of the loop in left ventricular hypertrophy (figs. 1 and 4). Thus as hypertrophy develops and the mass of muscle situated to the left and posteriorly increases, the distal position of the QRS sÊ-loop is directed upward and posteriorly. The reason that this distal rotation is not seen in the loops which resemble the normal type 2 loops may be due to the fact that these latter loops already bear some resemblance to the QRS sÊ-loop in left ventricular hypertrophy in being wide and sometimes inscribed in a counterclockwise direction in the frontal plane projection (fig. 3*c*). Secondly, despite the obvious lack of left axis deviation, the electrocardiograms of 24 of the 28 subjects were suggestive of left ventricular hypertrophy by conventional electrocardiographic criteria. Since these criteria include slight widening of the QRS complex and an intrinsicoid deflection beginning 0.04 second or more after the onset of the QRS, the electrocardiogram has an apparent clinical advantage over the vectorcardiogram as the latter does not readily show such temporal relationships or close correlation with the semidirect leads. The T sÊ-loops, however, were abnormal in size, shape and direction in the 20 records in which they were satisfactory for analysis. The spatial pattern of the T sÊ-loops was similar to that seen in the more typical records showing left ventricular hypertrophy. Finally, there was pathologic confirmation of the hypertrophy in two members of this group; each heart weighed 600 Gm. with left ventricular thicknesses of 1.8 and 2.0 cm., respectively.

There are several possible explanations for the normal appearance of 28 of the QRS sÊ-loops. As has been mentioned they may have represented an early stage in the development of the typical left ventricular hypertrophy pattern. It is also possible that concomitant right ventricular hypertrophy could have balanced the spatial forces and maintained a normal appearing resultant QRS sÊ-loop. Other possible factors which may have contributed to the normal appearance of the loops but which could not be evaluated were: (1) changes in the order of depolarization such that the resultant vector forces produced a recorded QRS sÊ-loop of normal appearance, (2) spatial cardiac position and (3) electrical field effects due to the extracardiac tissue either related to or independent of hypertrophy.

No significant correlation of the configuration of the QRS sÊ-loop with the etiologic type or clinical severity of heart disease was found. All 12 subjects who had QRS sÊ-loops which were similar to the type 1 normal loops had hypertensive and/or arteriosclerotic heart

disease. However, the group was not large enough for satisfactory analysis.

It has been proposed that the vectorcardiogram might suggest the diagnosis of left ventricular hypertrophy in instances where the electrocardiogram failed to do so.[8, 9] Because, with very few exceptions, electrocardiographic evidence of left ventricular hypertrophy was included among the criteria for selection of cases in this report, this problem cannot be investigated adequately with these data. In fact, as noted, there were instances in this series in which the converse was true.

Summary

1. The spatial vectorcardiograms in 90 subjects with left ventricular hypertrophy have been studied and described.

2. The configuration of the spatial vectorcardiogram in left ventricular hypertrophy was usually different from the normal. Typically the QRS sÊ-loop was smooth, wide and rounded, inscribed in a counterclockwise direction and placed largely to the left and above the isoelectric point in its frontal plane projection. The left sagittal plane projection of the QRS sÊ-loop was long, narrow and directed largely upward and posteriorly. The typical T sÊ-loop was small, smooth, horseshoe-shaped and counterclockwise in inscription in both frontal and left sagittal plane projections. In some instances the QRS sÊ-loop was similar to that of the normal but was always accompanied by an abnormal T sÊ-loop.

3. Concepts as to the genesis of the typical and variant configurations of the vectorcardiogram in left ventricular hypertrophy have been discussed.

4. Further study, including autopsy data, is required to define the spatial vectorcardiogram in left ventricular hypertrophy and associated disease of the myocardium and to establish the relative merits of the vectorcardiogram and the electrocardiogram in the evaluation of the state of the heart with left ventricular hypertrophy.

Sumario Español

1. Los vectorcardiogramas en 90 sujetos con hipertrofia ventricular izquierda han sido estudiados y descritos.

2. La configuración del vectorcardiograma espacial en hipertrofia ventricular izquierda fué usualmente diferente a lo normal. Tipicamente el anillo QRS sÊ fué suave, ancho y redondeado, inscrito en una dirección contraria al movimiento del reloj y localizado mayormente hacia la izquierda y arriba del punto isoeléctrico en su proyección en el plano frontal. La proyección de plano sagital izquierdo del anillo QRS sÊ fué larga, estrecha y dirigida mayormente hacia arriba y posteriormente. El anillo típico T sÊ fué pequeño, suave, con forma de herradura y en dirección contraria el movimiento de reloj en ambos planos de proyección frontal y sagital izquierdo. En algunas ocasiones el anillo QRS sÊ fué similar al normal pero estuvo siempre acompañado por un anillo anormal T sÊ.

3. Los conceptos sobre la génesis de las configuraciones típicas y variantes del vectorcardiograma en la hipertrofia ventricular izquierda se han discutido.

4. Más estudio, incluyendo datos de autopsia, se requieren para definir el vectorcardiograma espacial en la hipertrofia ventricular izquierda y en enfermedades similares del miocardio y para establecer los méritos relativos del vectorcardiograma y el electrocardiograma en la evaluación del estado cardíaco en la hipertrofia ventricular izquierda.

REFERENCES

[1] Duchosal, P. W., and Sulzer, R.: La Vectorcardiographie. Basel, S. Karger, 1949.

[2] Jouve, A., and Buisson, P.: La Vectorcardiographie en Clinique. Paris, Masson et Cie, 1950.

[3] Den Boer, W.: Vectorcardiographie Drukkery. Utrecht, Kemink en Zoon N. V., 1951.

[4] Grishman, A., and Scherlis, L.: Spatial Vectorcardiography. Philadelphia, Saunders, 1952.

[5] Podio, R. B.: Le Vectorcardiogramme unipolaire dans l'hypertrophie et le bloc de branche gauches. Arch. mal coeur **46:** 728, 1953.

[6] Burch, G. E., Abildskov, J. A., and Cronvich, J. A.: Spatial Vectorcardiography. Philadelphia, Lea & Febiger, 1953.

[7] —, —, and —: Studies of the spatial vectorcardiogram in normal man. Circulation **7:** 558, 1953.

[8] Pantridge, J. F., Abildskov, J. A., Burch, G. E., and Cronvich, J. A.: A study of the spatial vectorcardiogram in left bundle branch block. Circulation **1:** 893, 1950.

[9] Abildskov, J. A., Jackson, C. E., Burch, G. E., and Cronvich, J. A.: The spatial vectorcardiogram in right bundle branch block. Circulation **3:** 600, 1951.

Changes of Ventricular Impulse Formation during Carotid Pressure in Man

By M. Golbey, M.D., C. P. Ladopulos, M.D., F. H. Roth, M.D., and D. Scherf, M.D.

No proof exists that carotid sinus pressure influences ectopic automatic ventricular impulse formation in man. Two patients are described who revealed during carotid pressure slowing of a ventricular parasystolic focus and a change of the area of impulse formation respectively.

THERE appears to be general agreement that in the mammalian heart vagal stimulation has no effect on ventricular contractility. This was demonstrated by Drury[2] who used the myocardiograph of Cushny and was confirmed by optical determination of the intraventricular pressure of the artificially driven heart; when a cardiac alternans existed and weak faradic stimulation of the cardiac sympathetic nerves for a few seconds abolished the alternans and strengthened the contractions of the ventricle, stimulation of the vagus nerves with the strongest possible currents was devoid of effect.[10] Maximal stimulation of either vagus or of both simultaneously had no effect on ventricular excitability or conduction velocity of the dog heart.[6]

However, some instances are mentioned in the literature where vagal stimulation apparently has had an effect on ventricular ectopic impulse formation. Thus, a ventricular paroxysmal tachycardia was repeatedly abolished by carotid pressure.[19] In this case it may be argued that it was not the increase of vagus tonus during the carotid pressure, but the simultaneous decrease of sympathetic tonus[1] which caused the action. In a patient with complete A-V heart block, ventricular tachycardia and ventricular fibrillation were registered during attacks of the Stokes-Adams type.[17] These attacks appeared during straining at stool and could always be induced by gentle digital stimulation of the rectum. The action of an autonomic reflex can hardly be excluded and the vagus nerves may have played a part. The appearance of auricular or ventricular extrasystoles during carotid pressure is common.[15]

In the dog heart pretreated with aconitine, in amounts too small to cause any visible change in the electrocardiogram, brief faradic stimulation of the vagus nerve regularly led to the appearance of ventricular extrasystoles.[11] Once extrasystoles were present vagal stimulation increased their number. The possibility was discussed that acetylcholine formed in the auricle during vagus stimulation may cause this reaction in the ventricles.[11] It is known that under certain conditions in man, and in dogs under influence of aconitine, acetylcholine causes ventricular extrasystoles to appear.[13]

The effect of vagal stimulation on ventricular automaticity has been repeatedly investigated, and the older literature has been reviewed by Erlanger.[4] This author studied the chronotropic effect of the vagus during complete A-V block in the dog. He found an occasional but insignificant diminution of the rate "which developed slowly and reached its maximum later than the slowing of the auricles."

Similar results were obtained in two series of experiments performed on dogs, wherein complete A-V block was produced by severing the bundle of His or both bundle branches; prolonged vagal stimulation with strong faradic currents caused a slight but distinct slowing of the ectopic ventricular rhythm.[8, 9] However, in most experiments this action appeared after a latent period of three to five seconds, which makes a direct vagal effect improbable. Therefore these results were explained by the assumption mentioned above, namely, that acetylcholine, released in the auricle, is responsible for these minimal effects in the ventricles.[9]

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Finally, the rate of the ectopic beats in a case of parasystole was studied during the administration of atropine, digitalis, pilocarpine, Doryl (carbamylcholine chloride) and carotid sinus pressure.[3] During carotid sinus pressure a slowing effect on the ectopic ventricular centers could be calculated and this was interpreted as a result of direct action of the vagus.

In the present report two instances are described in which carotid sinus pressure influenced the automatic impulse formation in the ventricles with a clarity hitherto not described.

Clinical Observations

Observation 1. A 71 year old white man was admitted to the hospital for the fourth time because of shortness of breath and ankle edema. The heart was moderately enlarged, and a soft blowing systolic murmur was heard over the aortic and the apical areas. The blood pressure was 140/80. The electrocardiogram showed a sinus rhythm with frequent ectopic ventricular beats. The P-R interval was 0.24 second. Following administration of digitalis and salt-free diet marked improvement was noted.

It may be stated here that administration of digitalis leaf up to 0.1 Gm. daily caused characteristic RS-T segment changes, but did not modify the existing arrhythmia.

Analysis of the arrhythmia revealed the presence of ventricular parasystole. The ectopic beats appeared at different phases of diastole; sometimes they coincided with the normal QRS complex so that combination beats resulted when parts of the ventricles were activated by the sinus impulse and parts by the ventricular ectopic impulse. Often two ectopic beats appeared in succession, thus enabling us to determine directly the duration of the ectopic interval. When sinus beats appeared between two ectopic beats the interval between the latter was a multiple of an ectopic interval measured directly. Thus, all criteria are fulfilled for the diagnosis of parasystole.

Vector analysis revealed that the vectorcardiogram of the ectopic beat was displaced anteriorly, to the right and upward. The terminal portion of the ventricular loop was inscribed slowly and lay to the right and anterior to the zero point. This type of loop is similar to that seen in right bundle-branch block and indicates that the ectopic beat originated in the left ventricle.

Figure 1, like all other reproduced tracings of the patient shows lead II. The basic rhythm is a sinus rhythm with a rate of 75 per minute. Five ectopic beats are present and appear at different times during ventricular diastole. The ectopic intervals measure 346* (3 × 115 plus 1), 232 (2 × 115 plus 2) and 240 (2 × 115 plus 10). The ectopic interval directly measured on this day was 115. It varied on different days; it was as short as 86 and as long as 123.

Often series of ectopic beats appeared in succession (fig. 2). The longest series of uninterrupted ectopic beats numbered 60. Occasionally a sinus beat succeeded in reaching the ventricle as in figure 2*a*. After four ectopic beats with an interectopic interval of 100, a premature contraction appeared which was due to an aberrantly conducted sinus beat. The latter does not interfere with the ectopic rhythm which therefore was protected from outside impulses according to the rules of the parasystolic mechanism.

Figure 2*b* was taken while the patient was receiving digitalis. The P-R interval was still 0.24 second. In this tracing sinus beats interfered with ectopic beats and the ectopic interval was 86. The interval between the last ectopic beat of the first group (of three) and the first ectopic beat of the second group (of four) measures 254, which is almost exactly as much as three ectopic intervals.

Figure 2*c* shows a constant ectopic rhythm with an interval of 94. After the second, fifth and eleventh ectopic beats, abnormal beats appear, resembling the ectopic beats but representing, as in figure 2*a*, aberrantly conducted sinus beats.

While so far the tracings do not reveal anything unusual when compared with other instances of parasystole, the response to carotid pressure was quite abnormal. Invariably the ectopic rhythm was slowed down during the pressure and reached its normal values as soon as carotid pressure was interrupted.

* All figures represent hundredths of a second.

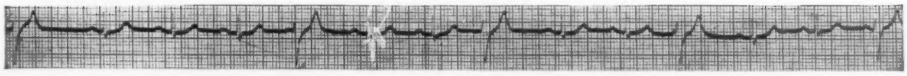

FIG. 1. Tracing showing parasystole with simple interference of two rhythms.

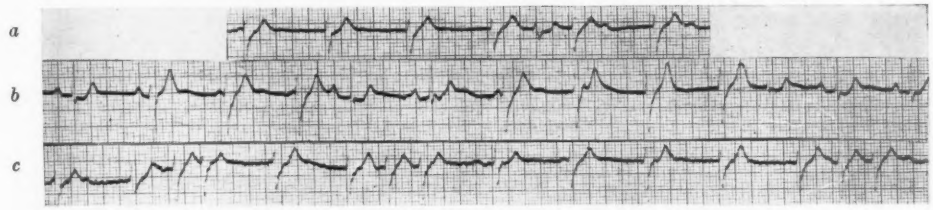

FIG. 2. Interference of ectopic rhythm with sinus beats. The latter are conducted within the ventricle in such a manner that they assume the shape of the ectopic beats.

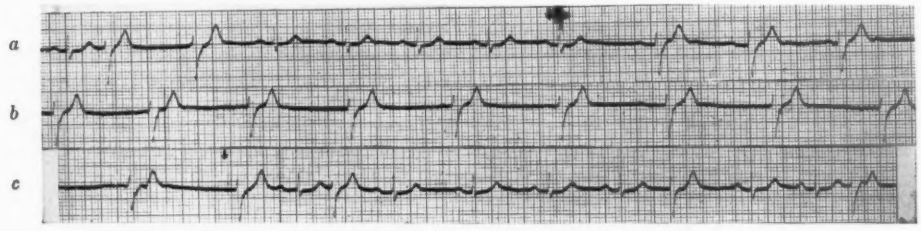

FIG. 3. Carotid sinus pressure causes slowing of ectopic rhythm. The three strips are continuous. At the beginning of the figure 3*a* two ectopic beats follow each other and permit measurement of the ectopic interval. It is 108. The arrows in figure 3*a* and figure 3*c* indicate the beginning and the end of the pressure on the right carotid sinus. During the pressure, the sinus node is inhibited, the sinus rhythm is suppressed and an undisturbed ectopic rhythm is registered, the ectopic interval being 112, 112, 112, 118, 120, 124, 126, 130, 132, 134, and 134. After termination of the carotid pressure (fig. 3*c*) a sinus beat is again seen between two ectopic beats, the ectopic interval measuring 112. The interval between the ectopic beats at the end of figure 3*c*, which are separated by two sinus beats measures 222, that is 2 × 111.

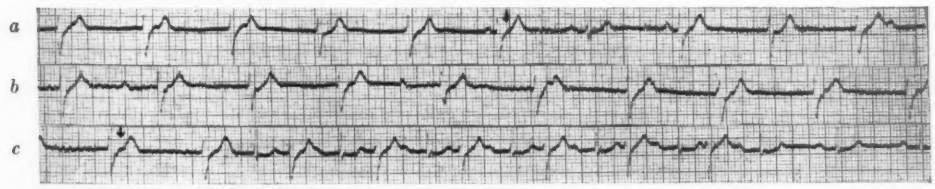

FIG. 4. Carotid pressure slows ectopic rhythm and, after it is discontinued, there is seen interference of ectopic, parasystolic rhythms with sinus rhythm simulating bigeminal rhythm. The three strips are continuous. The arrows again indicate beginning and end of the pressure. The ectopic intervals before the pressure in figure 4*a* were constantly 108. During the carotid pressure they measure: 110, 112, 112, 110, 116, 120, 112, 110, 128, 116, 116, 112, 116, 116, 116 and 116. On this occasion the pressure was on the left carotid sinus; usually, pressure on this side was less effective than on the right in prolonging the interectopic intervals.

Figure 3 shows such an experiment and figure 4 also represents the effect of carotid sinus pressure this time performed during the presence of an ectopic rhythm. The slowing of the ectopic rhythm during the carotid sinus pressure is obvious.

After discontinuation of carotid pressure in figure 4, an interesting picture appears with a

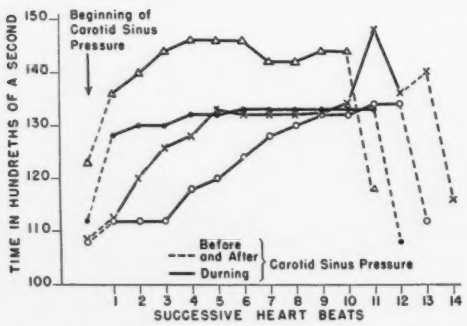

FIG. 5. Graph made from four tracings registered during carotid pressure illustrates the instantaneous slowing of the ectopic rhythm during the pressure and the quick return of the ectopic rate to normal after the carotid pressure is discontinued.

sinus beat interpolated between each group of ectopic beats without disturbing the ectopic rhythm. A bigeminal rhythm is simulated.

In figure 5 the result of carotid pressure obtained on four different occasions is reproduced. It is evident that the slowing of the ectopic impulse formation begins immediately after the onset of carotid pressure and quickly disappears after its discontinuation. The slowing of the rate amounted in one experiment to 31 per cent of its value before the carotid pressure.

Another interesting feature which could repeatedly be observed in this patient is depicted in figure 6. One must assume that the sinus beat broke into the ectopic center, disturbing its impulse formation. The protection of the ectopic center, which makes parasystole possible was broken. Actually, parasystole disappeared for a moment and the sinus beat disturbed the ectopic impulse formation as it always does in a normal heart. This phenomenon was observed repeatedly but only during carotid pressure, and in more than 30 tracings from this patient it was never seen spontaneously.

Observation 2. A 72 year old patient was admitted to the hospital with congestive cardiac failure and severe Cheyne-Stokes breathing due to coronary sclerosis. A complete A-V block was found, occasionally showing varying forms of ventricular extrasystoles and of automatic ventricular beats. Figure 7 shows the effect of right carotid sinus pressure. The four strips are continuous. Before the carotid pressure the tracing (lead III) shows complete heart block with ventricular complexes which remain identical. During carotid pressure the P waves disappear, the ectopic beats assume a different form and remain so until 14 seconds after the end of the pressure; with the appearance of a ventricular extrasystole the original ventricular automatic beats recur. The ectopic intervals in figure 7 measure: 188, 196, 192, 192, 192, 188, 192, 192, 192, 192. Pressure on the left carotid artery had the same effect.

This observation shows a distinct effect of carotid pressure on the activity of the ventricle. The change of form of the ventricular ectopic beats during carotid pressure could be explained

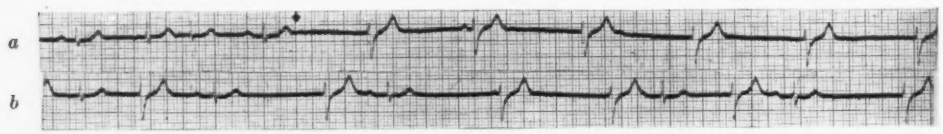

FIG. 6. Tracing illustrates break of protection of ectopic center during carotid pressure. Both tracings are continuous. In the beginning of the tracing two auricular extrasystoles appear. The arrow in figure 6*a* indicates the beginning of pressure on the right carotid sinus. The pressure was then continued throughout the tracing. As figure 6*a* shows, an ectopic rhythm appears with the typical slowing of the rate, the succeeding intervals being 128, 132, 134, 136 and 136. The last ectopic beat in figure 6*a* and the first one in figure 6*b* are followed by sinus beats. While the first sinus beat in figure 6*b* does not influence the interectopic interval, the second one does and so does the following one in the same strip. The ectopic interval at this time was 138 as measured between the last beat of figure 6*a* and the first ectopic beat in figure 6*b*, and also 138 as measured by the ectopic beats which succeed each other in the middle of figure 6*b*. The intervals between the first and second and between the second and third ectopic beats in figure 6*b* measure 228 and 216, which does not fit into the mechanism of parasystole. If, however, we measure, the distance between the second sinus beat and the following ectopic beat, it is 138; the same diastole is measured after the third sinus beat.

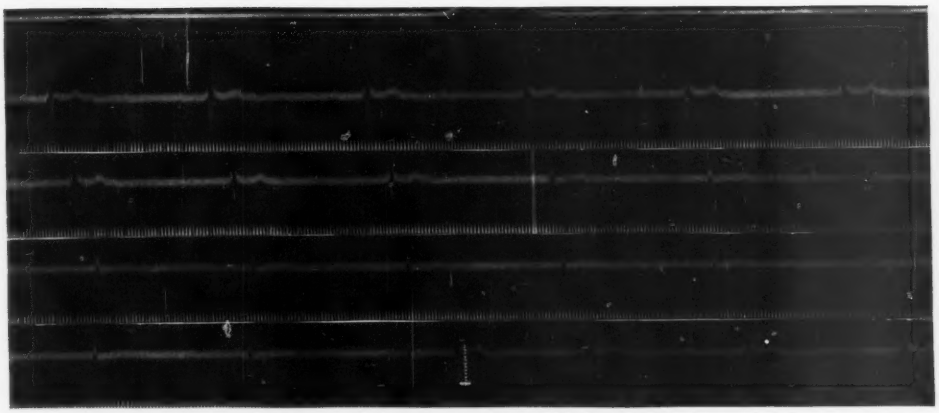

FIG. 7. Observation 2. Changes of form of idioventricular ectopic center in complete A–V block during carotid sinus pressure. The beginning of the carotid sinus pressure is marked by a signal, the end is indicated by the return of visible P waves in the electrocardiogram.

by shifting of focus or by disturbance of conduction. We are inclined to assume the first possibility. Changes of focus from beat to beat are known to occur in heart block and are explained by the presence of a bilateral bundle-branch block.[15] That the change of focus during carotid pressure was not fortuitous is demonstrated by the fact that it could repeatedly be elicited by carotid pressure while it was not observed in this form spontaneously.

It may be argued, that changes of form of the ventricular complexes without changes of rate speak in favor of a disturbance of conduction and against a change in the focus of impulse formation. It is however established that under different experimental conditions ventricular centers, situated in either ventricle form impulses with the same rate.[15, 16]

DISCUSSION

The tracings obtained in the first patient illustrate an instance of parasystole showing the following unusual features:

1. During carotid sinus pressure a pure ectopic rhythm was elicited, the basic rhythm being depressed.

2. During carotid sinus pressure there was progressive lengthening of the interectopic intervals, that is, slowing of the ectopic rhythm.

3. During carotid pressure, for a brief period a loss of the protection of the ectopic center from other impulses (protective block) occasionally was seen.

4. Arrhythmias appeared owing to the interference between ectopic and sinus rhythms which imitated bigeminal rhythms.

In the second patient carotid pressure led to the appearance of varying forms of ectopic beats with little or no change of rate. Whereas spontaneous changes or variations of the form of the ectopic ventricular beats were occasionally seen in this patient, the gradual change from the normal form as noted during carotid sinus pressure, and the return to normal when the pressure was discontinued were not seen spontaneously.

Thus in both subjects an effect of carotid pressure on ectopic ventricular impulse formation was observed; in observation 1 this effect was demonstrated more clearly than ever before. This was due to the fact that for the first time the lengthening of the ectopic intervals during carotid sinus pressure could be measured directly. We are fully aware that the observed changes during carotid pressure could be attributed to inhibition of the cardiac accelerator nerves, which has been demonstrated with the oscillograph during carotid pressure, and not to a vagal effect.[1] The immediate slowing of the heart after carotid pressure started and the rapid return of heart rate to the normal level when the pressure was discontinued (fig. 5) speak against an interpretation of the effect

of carotid pressure as a pure sympathetic nerve phenomenon. However, the possibility that the changes during carotid sinus pressure are caused by the release of acetylcholine in the auricle cannot be denied. The gradual increase of interectopic intervals and the fact that this increase occasionally lasts longer than the carotid pressure support this contention (fig. 3). An action of the carotid pressure on the coronary circulation could not explain these findings, for a vasoconstrictive effect upon it is unproven, and the changes could not appear so rapidly if the coronary circulation were involved.

The appearance in parasystole of an undisturbed ectopic rhythm during carotid sinus pressure has been observed clinically[7, 18] and experimentally.[14] Our first patient shows this phenomenon with rare clarity. The occasional break of the protection of the ectopic center, usually and, in our opinion, incorrectly named "protective block," has been observed previously.[12, 15] The fact that here it was observed only during carotid sinus pressure is of interest, but a discussion of the possibilities involved would be mere speculation.

The occasional appearance of a bigeminus-like rhythm in observation 1 (fig. 4) is fortuitous and does not permit the interpretation of a bigeminal rhythm on the basis of parasystole. This has been repeatedly attempted without success.

Conclusions

A patient with a classic type of ventricular parasystole is described. Carotid sinus pressure inhibited the sinus rhythm and permitted the ectopic parasystolic rhythm to proceed undisturbed. During carotid pressure the rate of the ectopic rhythm was slowed by as much as 31 per cent of its rate prior to carotid pressure. When carotid pressure was discontinued, the ectopic rhythm returned to its pre-existing rate.

Carotid sinus pressure also caused a break in the protection of the ectopic center (protective block). This phenomenon was seen several times during carotid pressure and never without it.

A patient with A-V block is described in whom carotid sinus pressure repeatedly caused the form of the ventricular complexes of the ectopic center to change without any change of rate. This phenomenon is explained by a shift of the pacemaker.

Sumario Español

Se describe un paciente con la variedad clásica de parasístole. La presión sobre el seno carótido inhibió el ritmo sinuoatrial y permitió el ritmo parasistolico ectópico prosequir sin interrupción. Durante la presión carótida la frecuencia del ritmo ectópico fué retardada por tanto como un 31 por ciento de su frecuencia antes de la presión sobre el seno carótido. Cuando la presión sobre el seno carótido fué descontinuada, el ritmo ectópico retornó a su frecuencia preexistente.

Presión sobre el seno carótido también causó una descontinuación del centro ectópico (bloqueo protector). Este fenomeno fué observado repetidas veces durante la presión sobre el seno pero nunca sin esta.

Un paciente con bloqueo A-V se describe en el cual la presión sobre el seno carótido repetidamente causó la forma de complejos ventriculares del centro ectópico cambiar sin producir cambio en la frecuencia del pulso. Este fenomeno se explica por un cambio en el pacificador del corazón.

References

[1] Bronk, D. W., Ferguson, L. K., and Solandt, D. Y.: Inhibition of cardiac accelerator impulses by the carotid sinus. Proc. Soc. exper. Biol. & Med. **31:** 579, 1934.

[2] Drury, A. N.: The influence of vagal stimulation upon the force of contraction, and the refractory period of ventricular muscle in the dog's heart. Heart **10:** 405, 1923.

[3] Eckey, P.: Untersuchungen ueber autonome Nervenwirkungen auf die Herzkammern des Menschen. Arch. Kreislaufforsch **5:** 1, 1939.

[4] Erlanger, J.: Ueber den Grad der Vaguswirkung auf die Kammern des Hundeherzens. Pflügers Arch. ges. Physiol. **127:** 77, 1909.

[5] Hoff, H. E., and Nahum, L. H.: The role of adrenaline in the production of ventricular rhythms and their suppression of acetyl-beta-methylcholine. J. Pharmacol. & Exper. Therap. **52:** 235, 1934.

[6] Hoffman, B. F., Siebens, A. A., and Brooks, C. M.: Effect of vagal stimulation on cardiac excitation. Am. J. Physiol. **169:** 377, 1952.

MUELLER, P., AND BARON, B.: Clinical studies on parasystole. Am. Heart J. **45:** 441, 1953.

PEKAR, M., AND LELKES, Z.: Einfluss der Vagusreizung auf den idioventriculaeren Rhythmus. Pflügers Arch. ges. Physiol. **238:** 66, 1936.

[10] PUDDU, V.: Beitraege zur Kenntnis der Herznervenwirkung. Pflügers Arch. ges. Physiol. **238:** 467, 1936.

[11] ROTHBERGER, C. J., AND SCHERF, D.: Wirkt der Vagus aur die Kontraktionsstaerke der Kammern des Saeugetierherzens? Ztschr. ges. exper. Med. **71:** 274, 1930.

[11] SCHERF, D.: Untersuchungen ueber die Entstehungsweise der Extrasystolen und der extrasystolischen Allorhythmien. Ztschr. ges. exper. Med. **65:** 198, 222, 225, 1929.

[12] —, AND BOYD, L. J.: Three unusual cases of parasystole. Am. Heart J. **39:** 650, 1950.

[13] —, AND CHICK, F. B.: Abnormal cardiac rhythms caused by acetylcholine. Circulation **3:** 764, 1951.

[14] —, AND —: Experimental parasystole. Am. Heart J. **42:** 212, 1951.

[15] —, AND SCHOTT, A.: Extrasystoles and Allied Arrhythmias, New York, Grune and Stratton, 1953.

[16] —, AND —: Ueber die Ursache des Formwechsels automatischer Kammerschlaege beim vollstaendigen Herzblock. Klin. Wchnschr. **11:** 945, 1932.

[17] SCOTT, R. W., AND SANCETTA, S. M.: Stokes-Adams attacks induced by rectal stimulation in a patient with complete heart block. Circulation **2:** 886, 1950.

[18] VEDOYA, R., DUMAS, J. J., AND URDOPILLETA, V.: Comentarios sobre dos casos de Parasistolia. Rev. argent. Cardiol. **15:** 364, 1948.

[19] WENCKEBACH, K. F., AND WINTERBERG, H.: Die unregelmaessige Herztaetigkeit. Leipzig, Engelmann, 1927.

Serum Lipid and Fat Tolerance Studies in Normal, Obese and Atherosclerotic Subjects

By JULIUS POMERANZE, M.D., WILLIAM H. BEINFIELD, M.D., AND MAX CHESSIN, B. S.

Fat tolerance tests demonstrated elevated and prolonged postprandial lipemia in markedly obese, hypercholesteremic, and atherosclerotic subjects when compared with normal individuals. An improvement of this abnormal fat tolerance was achieved following rigid fat restriction in hypercholesteremic and atherosclerotic subjects and following weight reduction in the extremely obese. An inferential relationship is suggested between extreme obesity and atherosclerosis.

DURING recent years greater availability of calories and the lessened necessity for their expenditure have brought about an increase in the incidence of obesity. Life insurance statistics and clinical studies revealingly document a relationship between obesity and atherosclerosis.[1] A statistically significant relationship has also been demonstrated between serum lipid and lipoprotein abnormalities and atherosclerosis.[2]

Certain biochemical abnormalities have been demonstrated in obesity and these have been related to atherogenesis. Postprandial hyperlipemia may persist in obese subjects.[3] A similar persistent hyperlipemia has been noted in atherosclerosis.[4] Hirsch and Carbonaro[5] found that the greatest percentage increase in serum fatty acids of normal subjects following a test fat meal occurred invariably in persons who tended to be obese and those who easily gained weight. An average weight loss of 19 pounds led to a significant reduction of the serum S_f 12–20, S_f 21–35, and S_f 35–100 lipoprotein fractions and total cholesterol in the majority of subjects of another experiment.[6] However, dietary fats as well as calories were drastically restricted. The effect of caloric restriction without fat restriction was not determined.

The following experiments were designed to determine the effect of a eucaloric, low-fat diet on serum lipids and fat tolerance in normal individuals, hyperlipemic individuals and elderly atherosclerotic individuals. Serum lipids and fat tolerance were similarly studied in obese subjects before and after weight reduction, following caloric restriction without rigid fat restriction.

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MATERIALS AND METHODS

Group 1 included five clinically normal male subjects, 20 to 40 years of age, of average weight, whose serum lipid values were within normal limits. Group II included four clinically normal male subjects, 20 to 40 years of age, of average weight, whose serum lipid values were considered abnormal. Group III included six male geriatric subjects over 70 years of age with positive clinical evidence of atherosclerosis Group IV was composed of 10 moderately obese subjects who were otherwise normal. There were seven females and three males in this group and all were less than 40 years of age. Group V was composed of 11 extremely obese subjects 20 to 40 years of age including eight males and three females, whose initial weights were 250 pounds or more.

A fat tolerance test was done on all subjects in groups I, II, III, and V initially. This consisted of giving the subjects 204 Gm. of fat in a test breakfast meal.* Blood was drawn serially during the follow-

* *Fatty Test Meal*

Amount	Food	Fat—Gm.
3	Egg yolks	18
1	Egg, whole	6
100 cc.	Hemog. cream (40%)	40
	Scrambled in	
6 pats	Butter	24
	Hot cereal and sugar	
4 pats	Butter	16
50 cc.	Heavy cream (40%)	20
2 slices	Bread	
4 pats	Butter	16
	Coffee and sugar	
50 cc.	Heavy cream (40%)	20
100 cc.	Milk } mixed	4
100 cc.	Cream (40%) } mixed	40
		204 Gm. = 6¾ oz.

ng 24 hours for biochemical determinations. There was no further intake of food during this 24-hour test period. Subjects of groups I, II, and III were then given a eucaloric diet containing less than 20 Gm. of fat per day for periods up to six weeks, and the fat tolerance test was repeated.

Those in group IV were observed for five weeks while ingesting a 1000 calorie diet containing 60 or more Gm. of fat per day. Serum cholesterol levels were determined serially.

Subjects on group V were permitted a 1200 to 1500 calorie diet daily which included at least 60 Gm. of fat. They were observed for periods up to 50 weeks. Total serum cholesterol was determined at regular intervals and fat tolerance studies were conducted both before and after weight reduction.

TABLE 1.—*Fat Tolerance Studies. Fasting Values and Values after a Test Meal of 204 Gm. Fat*

	Fasting	3 hrs.	5 hrs.	8 hrs.	12 hrs.	24 hrs.
Group I. Clinically Normal Males (20–40 years) with Normal Serum Lipids						
A.						
mg.% total cholesterol	252	238	236	238		248
phospholipids	294	318	326	341	302	298
total fatty acids	325	522	383	302	313	319
B. 6 weeks after eucaloric diet containing less than 20 Gm. of fat per day						
mg.% total cholesterol	211	202	214	214		208
phospholipids	238	250	272	248		243
total fatty acids	347	482	351			324
Group II. Clinically Normal Males (20–40 years) with Abnormal Serum Lipids						
A. Before low fat diet						
mg.% total cholesterol	306	308	305	300		303
phospholipids	242	265	294	298		262
total fatty acids	250	604	548	422	394	247
B. 6 weeks after eucaloric diet containing less than 20 Gm. of fat per day						
mg.% total cholesterol	202	205	200	198		201
phospholipids	194	216	231	228		208
total fatty acids	231	452	402	298	244	230
Group III. Male Subjects (70+ years) with Clinical Evidence of Atherosclerosis						
A. Before diet						
mg.% total cholesterol	182	194	202		196	195
phospholipids	206	252	300	402	309	214
total fatty acids	218	504	790	1100	432	226
B. 6 weeks following eucaloric diet containing less than 20 Gm. of fat per day						
mg.% total cholesterol	195	202	206	202	200	208
phospholipids	218	249	261	268	242	220
total fatty acids	254	588	704	810	318	252
Group IV. Extremely Obese (250 lbs. +) Male Individuals (20–40 years)						
A. Before weight reduction						
mg.% total cholesterol	206	190	198	200	202	214
phospholipids	262	274	291	282	261	261
total fatty acids	374	602	653	658	609	370
B. After 50+ weeks and weight loss greater than 50 lbs on a 1200–1500 calorie diet containing 60 Gm. of fat						
mg.% total cholesterol	209	215	202	198	203	206
phosphlipids	248	266	282	274	257	256
total fatty acids	266	362	374	338	299	254

TABLE 2

	Initial	1 wk.	3 wks.	5 wks.	15 wks.	50 wks.
Serum Cholesterol Levels (Mg.%) and Weight Changes (lbs.) in Moderately Obese Individuals on a Weight Reducing (60 Gm.) Fat Diet						
Group IV						
Weight	196	191.5	187	185		
Cholesterol	242	236	238	228		
Weight	241	235.5	230	228		
Cholesterol	202	224	218	220		
Weight	148	146	142	139		
Cholesterol	312	294	287	292		
Weight	218	208	204	201		
Cholesterol	212	206	218	232		
Weight	132	130	129	125		
Cholesterol	260	242	248	230		
Weight	184	180	175.5	170		
Cholesterol	302	287	288	282		
Weight	196	189	186	183		
Cholesterol	242	230	228	220		
Weight	166	163	159	155.5		
Cholesterol	284	296	279	294		
Weight	143	139	138	138		
Cholesterol	296	308	300	284		
Weight	196	186.5	182	179		
Cholesterol	198	204	202	196		
Serum Cholesterol Levels and Weight Changes in Extremely Obese Individuals on a Weight Reducing (60 Gm.) Fat Diet						
Group V						
Weight	296	284	—	275½	261	213
Cholesterol	198	214	—	204	196	210
Weight	305	302	—	287	—	—
Cholesterol	174	178	—	186	—	—
Weight	412	398	—	—	372	—
Cholesterol	208	232	—	—	218	—
Weight	291	—	—	—	—	—
Cholesterol	184	—	—	—	—	—
Weight	252	250	—	—	255	—
Cholesterol	209	219	—	—	216	—

TABLE 2—*Continued*

	Initial	1 wk.	3 wks.	5 wks.	15 wks.	50 wks
Group V—Continued						
Weight	264	259	—	246	233	198
Cholesterol	217	223	—	208	196	200
Weight	343	—	—	326	—	—
Cholesterol	184	—	—	204	—	—
Weight	266	261½	—	—	—	—
Cholesterol	248	232	—	—	—	—
Weight	288	274	—	261½	246	252
Cholesterol	202	194	—	190	186	204
Weight	273½	261	—	—	—	294
Cholesterol	212	—	—	—	—	218
Weight	250½	244	—	229½	221	203
Cholesterol	172	168	—	178	182	184

Total cholesterol was determined by the Schoenheimer-Sperry method.[7] Lipid phosphorus was measured by a modification of the Fisk and Subbarow method and converted to phospholipid by the factor 25.[8] Fatty acids were measured by a method described by Bauer and Hirsch.[9]

RESULTS

The pertinent data are summarized in tables 1 and 2.

A. Total Serum Cholesterol

Serum cholesterol levels in elderly individuals (group III) were found, as in previous studies,[10] to be relatively low. Similar low serum cholesterol levels were found in patients with extreme obesity (group V). The cholesterol levels in these elderly atherosclerotic individuals were unaffected by a eucaloric diet with rigid fat restriction. Weight loss with a low calorie (60 Gm.) fat diet in extremely obese subjects did not affect the relatively low serum cholesterol levels.

The serum cholesterol of normal and hypercholesteremic subjects was lowered by a rigidly fat restricted eucaloric diet. However, when these studies were continued for longer periods than those demonstrated in table 1, serum cholesterol rose toward pretreatment levels despite the continuance of the low fat diet. It

was extremely difficult to maintain subjects on this low fat diet for a period longer than six weeks.

In none of the groups was the serum cholesterol value altered in the acute experiment following the intake of a breakfast meal containing 204 Gm. of fat.

B. Phospholipids

During the low-fat, eucaloric diet study, serum phospholipids followed the pattern of serum cholesterol in the normal individuals and the cholesterol-phospholipid ratio was similar before and at the end of six weeks. In the hyperlipemic individuals the fall in phospholipid levels did not approximate the fall in cholesterol levels and the cholesterol-phospholipid ratio was lowered. In the subjects in the old age groups the phospholipid levels, similar to the cholesterol levels, were not significantly changed by six weeks on the eucaloric low-fat diet. Weight reduction without fat restriction had little effect on phospholipid levels in extremely obese individuals.

During the acute experiment in which subjects ingested 204 Gm. of fat in the breakfast meal, phospholipids rose moderately in all groups. Lipemia occurred despite the lowered cholesterol-phospholipid ratio during these acute experiments.

C. Serum Fatty Acids

Fatty acids were low in the elderly atherosclerotic individuals as were all other lipid fractions. Serum fatty acids were moderately elevated in extremely obese individuals although all other lipid fractions were low.

The lipemic response to the fat meal appeared to yield more information. In normal subjects, serum fatty acids, rose moderately following the ingestion of 204 Gm. of fat in the test breakfast. Within eight hours these had returned to fasting levels. In the hyperlipemic subjects, although fasting fatty acids were lower than in normals, they rose considerably higher and were maintained above the postabsorptive level longer than 12 hours. A high and prolonged elevation of fatty acid was demonstrated in group III (elderly atherosclerosis). Group V (extreme obesity) exhibited a prolonged elevation of fatty acids following the test breakfast.

In groups I, II, and III a eucaloric diet with rigid fat restriction and in group V, weight loss without rigid fat restriction, caused a change in the fat tolerance curve. The change consisted in the serum fatty acids not reaching as high levels as previously and returning more rapidly to postabsorptive levels.

Discussion

The importance of the relationship of hypercholesteremia to experimental atherosclerosis in animals encouraged attempts to establish a similar relationship in man. Although numerous investigations have failed to clearly confirm hypercholesteremia as atherogenic in the human, frequent attempts have been made to alter serum cholesterol levels by dietary means. The present data reveal that serum cholesterol is significantly lowered by rigid fat restriction even when sufficient calories are provided to prevent loss of weight. When experiments are continued beyond the six weeks of the present study, continued fat restriction fails to maintain the fall in serum cholesterol previously established.

Previous investigations of obesity and serum lipids have been concerned largely with the effect of the reduction of fat intake coincident with caloric restriction.[6] Our investigation of weight loss without extreme fat restriction, indicates that there is no effect of simple caloric restriction on serum cholesterol values.

Serum cholesterol is unaltered by rigid fat restriction in the elderly patient with initially low levels. Other lipid fractions usually follow a pattern similar to cholesterol changes.

These experiments clearly indicate that serum cholesterol levels are unaffected by the acute intake of large amounts of fat and cholesterol.

The theory has been advanced[11] that the gradual development of atherosclerosis in otherwise normal human beings may be the direct result of recurrent alimentary chylomicronemia due to repeated ingestion of many fatty meals over a lifetime; prolonged postprandial lipemia is considered the atherogenic factor. Physiologic postprandial lipemia reaches

its peak within five hours and does not persist beyond eight hours. Prolonged postprandial lipemia was observed in groups I, II, III, and V. A more normal fat tolerance was obtained following rigid fat restriction in groups I, II, and III, and following weight reduction in group V.

Summary

Hypercholesteremia is affected by severely fat restricted eucaloric diets although no weight loss is evidenced. Weight reduction without rigid fat restriction appeared not to affect serum cholesterol levels.

Elevations and prolongations in elevation of postprandial serum fatty acids were observed in hypercholesteremic, elderly atherosclerotic and extremely obese individuals. This abnormal fat tolerance was improved in hypercholesteremic and elderly atherosclerotic subjects following rigid fat restriction and in extremely obese subjects following weight reduction. If postprandial hyperlipemia is an atherogenic factor and its alteration is affected by weight reduction, these observations provide further evidence of the value of weight reduction for the prevention of atherosclerosis.

Sumario Español

La hipercolesterolemia es afectada por la restricción severa de grasas en dietas eucalóricas aunque pérdida en peso no ocurrió. La reducción de peso sin restricción rígida de grasas aparentemente no afecto el nivel de colesterol en el suero.

Elevaciones y prolongaciones en la elevación de los ácidos grasos postprandiales fueron observadas en individuos de edad madura, hipercolesterolémicos y extremadamente obesos. Esta tolerancia anormal a las grasas fué mejorada en individuos de edad madura, hipercolesterolémicos y ateroescleróticos sometidos a una dieta con restricción rígida de grasas y en sujetos sumamente obesos sometidos a una reducción en peso. Si la hiperlipemia postprandial es un factor aterogénico y su alteración es afectada por reducción en peso, estas observaciones proveen más evidencia del valor de la reducción en peso en la prevención de la ateroesclerosis.

References

[1] Armstrong, D. B., Dublin, L. I., and Wheatley, G. M.: Obesity and its relation to health and disease. J. A M. A. **147:** 1007, 1951.

[2a] Pomeranze, J., and Kunkel, H. G.: Serum lipids in diabetes mellitus. Proc. Am. Diab. A. **10:** 217, 1950.

[b] Gubner, R., and Ungerleider, H. W.: Arteriosclerosis, a statement of a problem. Am. J. Med. **6:** 10, 1949.

[c] Gofman, J. W., Jones, H. B., Lindgren, B. S., Lyon, T. P., Elliot, H. A., and Strisower, B.: Blood lipids and human atherosclerosis. Circulation **2:** 161, 1950.

[3] Thannhausser, S. J.: Serum lipids and their value in diagnosis. New England J. Med. **237:** 515, 1947.

[4] Pomeranze, J., and Beinfield, W. H.: Fat tolerance relationship to atherosclerosis. Bull, New York M. Coll. **14:** 70, 1951.

[5] Hirsch, E. F., and Carbonaro, L.: Serum esterified fatty acids with fat tolerance tests in diabetes mellitus. Arch. Int. Med. **86:** 519, 1950.

[6] Walker, W. J., Lawry, E. Y., Love, D. E., Mann, G. E., Levine, S. A., and Stare, F. J.: Effect of weight reduction and caloric balance on serum lipoprotein and cholesterol levels. Am. J. Med. **14:** 654, 1953.

[7] Schoenheimer, R., and Sperry, W. M.: A micromethod for determination of free and combined cholesterol. J. Biol. Chem. **106:** 745, 1935.

[8] Fiske, C. H., and Subbarow, Y.: Colorimetric determination of phosphorus. J. Biol. Chem. **66:** 375, 1925.

[9] Bauer, F. C. Jr., and Hirsch, E. F.: A new method for the colorimetric determination of the total esterified fatty acids in human serum. Arch. Biochem. **20:** 242, 1949.

[10] Pomeranze, J., Boyd, L. J., and Goldbloom, A. A.: Clinical studies in geriatrics. 1. Serum lipid partitions. Arch. Int. Med. **91:** 740, 1953.

[11] Moreton, J. R.: Chylomicronemia, fat tolerance and atherosclerosis. J. Lab. & Clin. Med. **35:** 373, 1950.

CLINICAL PROGRESS

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Myocarditis

By CLARENCE E. DE LA CHAPELLE, M.D., AND CHARLES E. KOSSMANN, M.D.

IN THE PAST, many practicing physicians in this country as well as abroad designated almost every disease of the heart muscle as "myocarditis." In the majority, the disease was probably replacement fibrosis of the myocardium. The latter was undoubtedly the result of coronary arteriosclerosis or of an inadequate coronary blood supply to a myocardium hypertrophied by arterial hypertension.

In time the pendulum swung to the other extreme. Few clinicians made a diagnosis of myocarditis except in the presence of rheumatic fever even though many of them were aware of the present-day meaning of the term, namely, inflammation of the myocardium.

Data assembled in the past 10 to 15 years show that myocarditis is not uncommon at postmortem examination. Therefore, the lesion cannot be a rarity in clinical medicine. The one individual who has made physicians aware of this fact by means of his splendid, meticulous pathologic studies and reviews is Saphir.[1, 2, 9, 14] Renewed interest in the clinical recognition of myocarditis has also been stimulated by the innumerable reports of electrocardiographic abnormalities, particularly in the presence of acute infectious diseases, from military hospitals during and following World War II. The rather liberal use of the electrocardiograph in the clinical work-up of patients in the hospitals of the Armed Forces undoubtedly contributed to the frequency of these reports. Two diseases which occurred among our troops in two entirely different parts of the globe, namely, scrub typhus fever in the South Pacific and diphtheria in Central Europe, are examples in which electrocardiographic studies elicited much valuable information and stimulated more frequent clinical recognition of myocardial involvement in these two diseases.

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PATHOLOGIC INCIDENCE

As seen in the accompanying table (table 1) from Saphir and Gore,[1, 2] based on a review of 1402 cases of myocarditis verified by pathologic examination, myocarditis occurs in practically every type of acute disease and with a wide variety of etiologic agents. These cases were studied between 1942 and 1946 when more than 40,000 autopsies were recorded at the Armed Forces Institute of Pathology.[3]

The incidence of myocarditis in 1250 consecutive necropsies, exclusive of fetal and neonatal deaths and medical examiner's cases, performed at Bellevue Hospital between January 1951 and December 1952 was only 3.3 per cent. The number of sections for microscopic examination taken from each heart ranged from 3 to 15 in the 42 cases analyzed.

No. of Cases	Age	Sex		Race	
		Male	Female	White	Colored
2	11–20	2	0	2	0
4	21–30	0	4	3	1
3	31–40	2	1	3	0
8	41–50	3	5	7	1
9	51–60	8	1	6	3
12	61–70	8	4	11	1
4	71–80	3	1	4	0
Total 42		26	16	36	6

In 13 of the 42 cases the myocarditis was associated with acute or subacute bacterial

TABLE 1.—*Diseases Associated with Myocarditis* (From Gore and Saphir, 1948)*

	Column 1	Column 2		Column 1	Column 2
Rickettsial diseases			Septicemia		
Scrub typhus	227	227	Streptococcus	11	23
Epidemic typhus	23	48	Staphylococcus	34	107
Rocky Mountain spotted fever	9	19	Pneumococcus	9	18
Diphtheria	144	221	Other acute bacteremias	15	Unknown
Subacute bacterial endocarditis	208	208			
Rheumatic heart disease	130	130	Acute glomerulonephritis	14	160
Meningococcemia	111	256	Acute tonsillitis	12	Unknown
Scarlet fever	24	44	Acute nasopharyngitis	41	Unknown
			Cellulitis, lymphangitis, and wound infections	13	Unknown
Weil's disease	7	8			
Relapsing fever	6	11			
Syphilis (gummatous)	2	66	Tularemia	1	16
			Brucellosis	2	4
Chagas' disease	1	1	Miscellaneous (postinfectious)	13	Unknown
Schistosomiasis	5	41			
Malaria	5	135	Exfoliative dermatitis	7	44
Trichinosis	2	2	Arsenical reaction	1	18
			Sulfonamide hypersensitivity	105	Unknown
Acute encephalitis	13	144			
Poliomyelitis	13	94	Disease unknown (so-called "idiopathic")	43	
Infectious mononucleosis	6	9			
Measles					
Guillain-Barré syndrome	3	30	Starvation	33	50
Mumps	1	8			
Epidemic hepatitis	1	400	Heat stroke		
Smallpox	1	9	Surviving less than 24 nours	16	45
Virus pneumonia	32	222	Surviving more than 24 hours	13	26
			Carbon monoxide poisoning (limited to patients who survived for an appreciable interval after the lethal exposure)	1	30
Tuberculosis	9	581			
Boeck's sarcoid	3	12			
Coccidioidomycosis	11	48			
Blastomycosis	2	5			
Actinomycosis	1	9	Emetine	1	70
Torulosis	1	6	Burns	11	45
			Total	1402	

* The figures in the first column represent the number of times myocarditis was encountered. Wherever possible the number of cases of each disease, screened to ascertain the first figure, is given in column 2. The ratio of the two thus provides a crude index of the frequency of myocarditis in each disease.

endocarditis, and in nine it was part of a rheumatic carditis. In eight cases myocarditis was found in association with sepsis or pyemia. The remaining 12 cases presented myocardial inflammatory changes in a variety of diseases including tuberculosis, glomerulonephritis, granulomatous infections, disseminated lupus erythematosus, fungus infection (aspergillosis), bronchiectasis, and lobular pneumonia. In two instances the question of alkalosis and electrolyte imbalance and hypersensitivity to sulfonamide therapy arose as possible causes of the myocarditis. No instances of so-called Fiedler's (isolated) myocarditis were met with in this group.

Of the 42 cases, 16 were in the age group from 61 to 80 years, and 17 were in the period from 41 to 60 years. Therefore, 33, or the majority, were above the age of 40 years. Although Bellevue Hospital has a pediatric service, no children came to necropsy with any evidence of myocarditis during this period of two years when the 1250 postmortem examinations were

performed. The youngest adult with myocarditis was 19 years old.

There were 26 males and 16 females in the group. The usual ratio of males to females in Bellevue Hospital necropsies is 2:1. Only six Negroes were represented as compared to 36 white; among the latter were two white Puerto Ricans and one Chinese.

Some four of the 42 were considered to have died unexpectedly although they were seriously ill at the time of death.

Myocardial involvement was not recognized clinically in the majority of the 42 cases. In the 13 cases of acute and subacute bacterial endocarditis the correct diagnosis of the "endocarditis" was made in only six. In none of the 13 was mention made of myocarditis in the final clinical diagnosis. In contrast, one-half of the rheumatic cardiac patients were considered to have "active myocarditis." Two who were submitted to mitral commissurotomy were found to have rather widespread rheumatic myocarditis involving not only the auricular appendages, so commonly seen in biopsy specimens taken at the time of operation, but also the myocardium of the ventricles.[4] Clinically both patients were considered to be free of rheumatic infection.

Practically no patients with communicable diseases are admitted to Bellevue Hospital. We, therefore, reviewed 1000 necropsies performed at Willard Parker Hospital, a municipal institution for the care of communicable diseases in New York, in the period from 1932 to 1952. Seventy-eight cases of myocarditis were disclosed, or an incidence of 7.8 per cent. This is readily accounted for by the known high incidence of myocarditis in the type of infectious diseases admitted to this hospital.

Analysis of these 78 autopsies reveals the largest number of cases with myocarditis, as determined histologically, namely 18, in individuals with diphtheria. Fourteen occurred in poliomyelitis, and 14 also were found in patients presenting various forms of tuberculosis. Nine were associated with measles, seven with scarlet fever, six with meningococcemia or meningococcus meningitis, and only two in pertussis. Six of the remaining eight cases of myocarditis occurred in a variety of diseases including pneumonia, otitis media, influenza meningitis, aplastic anemia, croup with tetany, and erythema multiforme bullosum. There were two instances of isolated myocarditis.

The incidence of myocarditis is known to be unusually high in poliomyelitis and diphtheria.[5] In the former an incidence of 100 per cent has been reported in some epidemics (1949).[6] Dolgopol,[7] while pathologist to Willard Parker Hospital, published a review of cases of poliomyelitis coming to postmortem examination and found an incidence of 26.6 per cent. The experience with diphtheritic myocarditis in this hospital was reported in considerable detail by Burkhardt and his associates.[8]

These data from a large general hospital and a hospital for contagious diseases compare with an incidence of 4.3 per cent among 5626 autopsies performed at the Michael Reese Hospital, reported by Saphir,[9] and is in contrast to a 9 per cent incidence found by the same observer at the same hospital in a study of 1000 other consecutive autopsies when more (about 25) than the usual number of blocks were taken from each heart for microscopic examination.

In summary, the pathologic data indicate the likelihood that the over-all incidence of myocarditis is approximately 10 per cent. This takes for granted, however, that all individuals, including children, dying of infections of bacterial, viral, protozoal, rickettsial, helminthic and fungal origin are included. In addition, this figure will obtain only if multiple sections of the heart, more particularly of the myocardium, are examined histologically.

Clinical Incidence

The incidence of myocarditis as based on clinical recognition is distinctly lower than the pathologic incidence. Having failed to find any recent figures on this problem, particularly analyses made since the advent of multiple electrocardiographic records, including precordial and extremity leads, we turned to the clinical records of Bellevue Hospital to seek an answer. This large municipal hospital is affiliated with four medical schools whose faculties are responsible for the diagnostic work-up and care of all the patients. Here we found that a

diagnosis of myocarditis was made only 16 times among 68,000 discharged patients in 1952, an incidence of 0.02 per cent. This includes 11 patients diagnosed as "rheumatic myocarditis, active," two patients with a diagnosis of "acute isolated myocarditis, unknown cause," one patient with "idiopathic myocarditis," and finally, one case of "acute bacterial myocarditis" and one of "subacute bacterial myocarditis."

Since, as already mentioned, Bellevue Hospital admits practically no communicable diseases, we obtained some figures from the record files of Willard Parker Hospital which is mainly for the care of such diseases. Among 4946 discharges during the year 1951, no diagnosis of myocarditis was noted, but during 1952 among 6452 discharges one diagnosis of "acute myocarditis complicating meningococcemia" was made and proved to be correct at necropsy.

From these figures, it is quite obvious that pathologists recognize myocarditis at necropsy far more frequently than physicians diagnose it during life. The discrepancy suggests that the signs and symptoms of myocarditis are frequently overshadowed by those of the primary disease, or indeed, that they are completely lacking in many instances. It is also probable that myocarditis is common in many diseases but is of such a mild degree that it is not recognizable. In most of these instances, recovery is the rule. How many of those who recover have residual myocardial changes is a moot question. Some of the areas of myocardial fibrosis seen at necropsy without sufficient reason for their presence may represent the residual scars of previous inflammatory reactions.

Definition

The term "myocarditis" as used pathologically should be limited to hearts which demonstrate evidence of acute, subacute or chronic inflammation of the myocardium, either focal or diffuse. If no active inflammatory process is found in the myocardium the term should not be employed. An important exception is diphtheritic myocarditis in which, during the early course of the disease, no inflammatory cellular infiltrate is seen. The lesion, during that period, is mainly a parenchymatous one.

According to Karsner[10] "acute myocarditis" to the pathologist "indicates a condition in which there is, associated with muscle degeneration or necrosis, an infiltration into the interstitial tissues of cells usually found either in acute or subacute exudative processes." He does not believe that a differentiation between acute parenchymatous and acute interstitial myocarditis is justifiable.

In those instances in which fibrous tissue is present, especially if it is interstitial in distribution and also if there is scarring of muscle bundles, "myocardial fibrosis" is apt to be the proper designation. If, on the other hand, the scarring is of perivascular distribution, then the lesion is most likely postinflammatory in nature, and commonly the end result of rheumatic myocarditis. In such instances collection of residual inflammatory cells may be seen. Sections of this description usually represent "healed myocarditis."

Pathologic Features

The diagnosis of myocarditis usually requires examination of multiple sections from various parts of the myocardium. Gross recognition of myocarditis is usually difficult, often impossible. Sometimes the heart may be flabby or pallid or yellowish with dilated chambers. Mural thrombi may be present. However, in many instances the heart appears normal.

Microscopically, there may be found interstitial infiltrations of histiocytes, lymphocytes and eosinophilic or neutrophilic polymorphonuclear leukocytes between the muscle fibers and in the perivascular connective tissue. In some sections the muscle fibers may exhibit fatty, granular, or hyaline degeneration. Focal embolic lesions or focal intrafascicular infiltration of inflammatory cells may be seen in the myocardium in the presence of acute and subacute bacterial endocarditis.

In bacteremia, especially when the Staphylococcus is the etiologic organism, abscesses, usually microscopic in extent, are not uncommonly encountered. These lesions are usually found in relation to terminal branches of the coronary arteries.

In idiopathic myocarditis, also known as Fiedler's or interstitial myocarditis, the inflammatory changes are limited to the myocardium, hence the frequent designation "isolated" myocarditis. In the early stages, the heart may present softening, areas of fatty change and zones of hyperemia. Mural thrombi, usually intraventricular, are commonly found.

Histologically there may be seen diffuse bands of lymphocytes, histiocytes, plasma cells, and occasionally eosinophils. Sometimes nucleated giant cells are recognized similar to those found in the granulomata of syphilis and tuberculosis. In conjunction with this cellular response there may be disseminated areas of necrosis as well as areas of replacement fibrosis.

A similar microscopic picture is said to occur in the myocardium as the result of hypersensitivity to sulfonamide drugs[11-13] or as an allergic response to the administration of penicillin, serum, or other sensitizing agents.

It is now generally accepted that a so-called virus myocarditis occurs not infrequently in such viral or suspected viral diseases as anterior poliomyelitis, infectious mononucleosis, varicella, infectious hepatitis, measles, mumps, atypical primary pneumonia and several others.[14] Histologically, the lesion includes a focal or diffuse invasion of the interstitial tissue mainly by lymphocytes, and less numerous as a rule are the polymorphonuclear leukocytes. In some instances only lymphocytes and monocytes are seen. Plasma cells are rarely seen in this type of myocarditis; likewise necrosis of muscle fibers does not seem to be a prominent feature.

The virus of poliomyelitis has been isolated[15] from the hearts of patients dying of poliomyelitis. Although this has not been confirmed by other observers, there are authentic reports[16, 17] of a virus having been isolated from anthropoid apes who apparently died from myocarditis. It was possible to produce practically identical myocardial lesions with this virus in mice and guinea pigs. This virus has come to be known as the "encephalomyocarditis (EMC)" virus.[18] Three instances of this disease in man have been reviewed.[19]

Among the infectious granulomata of the heart are included syphilis and tuberculosis, but they rarely involve the myocardium. The latter is most frequently seen as microscopic miliary tubercles occurring in the presence of generalized miliary tuberculosis, or as an extension from tuberculous mediastinal lymph nodes. Rarely, nodular tuberculomata may be found in the myocardium. Other granulomata which may be seen in the myocardium include actinomycosis which usually extends from the mediastinum or lung, and in which lesion the ray fungus is readily demonstrated; and sarcoidosis, which may produce rather typical interstitial or intrafascicular lesions simulating tuberculous granulomata.

Trichinosis may cause myocarditis in the form of a diffuse infiltration of polymorphonuclear leukocytes, plasma cells, and sometimes of eosinophils. The parasites, although usually not detectable, may be recovered following digestion of a fresh specimen.

In Chagas' disease, seen principally in Brazil but also in other Latin American countries, the protozoans (*Trypanosoma cruzi*) may lodge in the myocardium and cause necrosis and inflammation of the interstitial tissue.

In malaria the plasmodium, usually Falciparum, may produce thrombi in the capillaries of the myocardium with resultant ischemic changes in the muscle fibers. The parasites may be seen in these capillaries together with agglutinated erythrocytes.

Classification

Myocarditis may be acute, subacute, or chronic, the differentiation being made arbitrarily on the basis of duration. Chronic myocarditis, when employed in the true sense of the term, implies continued activity, or at least frequent recurrences, of the inflammatory process over an appreciable period of time. The most common cause of the latter type of myocarditis is rheumatic fever.

Saphir[2] has proposed a useful working classification of myocarditis which includes four main types: (a) myocarditis following infectious diseases, with or without endocarditis; (b) the specific type with characteristic anatomic structure, or identifiable pathogenic organism (rheumatic fever, tuberculosis, blastomycosis,

Chagas' disease, and other conditions); (c) those due to chemical poisons, physical agents, or hypersensitive states; and (d) the isolated type, unassociated with any known illness. In another classification suggested by Friedberg[20] myocarditis is divided into: (1) infectious and toxic myocarditis; (2) suppurative myocarditis; and (3) idiopathic or isolated (Fiedler's) myocarditis.

Clinical Diagnosis

The diagnosis of myocarditis is made mainly by inference in the presence of one of the many types of diseases previously enumerated.

According to the fifth edition of the "Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels"[21] the diagnostic signs of myocarditis include the following:

> Sinus tachycardia. Abnormal rhythms. Enlargement of the heart. Systolic murmur at apex due to mitral incompetency. Faintness or sharp quality of the first heart sound. Evidence of cardiac insufficiency. Electrocardiographic changes such as defective atrioventricular or intraventricular conduction, or S-T and T-wave changes. Fever. Leukocytosis. Increased sedimentation rate.

Symptoms of myocarditis are by no means specific. In fact they are not infrequently very slight or completely absent. Frequently the symptoms are caused by the primary disease rather than by the myocarditis. Occasionally patients complain of vague aches and pains over the precordial area which have no relation to physical effort, appearing even at rest in bed, and of variable duration, ranging from minutes to hours. No particular type of radiation has been described.

Some patients complain of palpitation both with and without any appreciable increase in heart rate or arrhythmia. Weakness and fatigue seem to be relatively common complaints; less often anorexia or headaches are mentioned.

When heart failure intervenes as it does in those cases of myocarditis with rather severe myocardial inflammation, then the symptoms are the same as those met with in any instance of heart failure. It occurs quite often in the presence of rheumatic myocarditis but is also common in "isolated" myocarditis and not infrequently in that associated with diphtheria and with bacterial endocarditis. In the absence of valvular disease, it definitely indicates the presence of myocarditis, taking for granted, of course, that the patient is in the midst of an infection or convalescing from one.

The usual complaints when heart failure intervenes include dyspnea and orthopnea. Occasionally, however, the picture is confused by the presence of shock, the result of peripheral vascular collapse, which is not a rare occurrence in the presence of the severe and toxic types of acute infectious disease. It may occur with little or no impairment of the myocardium and, therefore, cannot be considered a symptom indicative of myocarditis except possibly in the case of diphtheritic myocarditis.

Sinus Tachycardia in the cases we have reviewed was not common and could readily be due in many instances to the primary disease rather than to the myocarditis, per se. However, in patients with acute rheumatic fever associated with myocarditis, it is rather common to have a tachycardia, and particularly one which is out of proportion to the height of the fever. On the other hand bradycardia may occur in the presence of myocarditis, including that caused by rheumatic fever. It has been noted quite frequently in children and young adults (fig. 2) after the first week or two of the illness[22] and has been ascribed by some to overactivity of the vagus. Bradycardia is also said to be observed often in primary atypical pneumonia.[4] All patients with bradycardia in whom myocarditis is suspected should be checked by electrocardiogram in order to rule out heart block, which is not uncommon in several types of myocarditis, including that occurring in diphtheria,[5, 23] rheumatic fever[24] and Chagas' disease.[25]

Abnormal Rhythms, including premature ventricular systoles, paroxysmal supraventricular tachycardia, atrial fibrillation, atrial flutter and idioventricular rhythm, have been described as occurring in the presence of myocarditis. Rheumatic myocarditis seems to have the greatest incidence of rhythmic disturbances,

but diphtheritic myocarditis is also known to be complicated by a number.[26, 27]

On occasion the appearance of an arrhythmia in the presence of an acute infectious disease will arouse the first suspicion of an underlying myocarditis or lead to the taking of an electrocardiogram which in turn may furnish information suggestive of myocardial disease.

Enlargement of the Heart. In many instances of myocarditis the heart is of normal size. When obvious enlargement is found at the bedside it is likely that the patient has a rather severe and diffuse myocarditis. In such instances it is often transient and may recede rather rapidly, although in Fiedler's (isolated) myocarditis it usually persists and progresses.

The material which has been reviewed would indicate that enlargement of the heart in myocarditis is clinically not common. The heart is most apt to enlarge in the presence of rheumatic, diphtheritic and chagasic myocarditis among the specific myocarditides, and in Fiedler's (isolated) myocarditis among those of unknown origin.

Systolic Murmur at Apex Due to Mitral Incompetency. An apical systolic murmur is a rather common finding in myocarditis but is by no means conclusive evidence of an inflamed myocardium. Sometimes it appears only when heart failure intervenes, at other times it seems to accompany the elevation of temperature, and occasionally it may parallel the presence of anemia. In those cases of acute and subacute bacterial endocarditis with complicating myocarditis or with focal abscesses of the myocardium, a systolic murmur at the apex may be the result of underlying pre-existing valvular deformity, or of destruction of the valve cusp by the vegetative process, or finally as a sign of myocardial failure.

Diastolic murmurs, either at the aortic or mitral areas, are rare in uncomplicated cases of myocarditis. They are most apt to be heard in children with rheumatic carditis associated with aortic or mitral valvulitis or both. Even in these circumstances they may be transient, disappearing after the carditis has subsided.

Faintness or Sharp Quality of the First Heart Sound. Normal heart sounds have been described in many instances of proven myocarditis, possibly in the majority. However, among the fairly common signs elicited on physical examination has been a faint, muffled or impure first sound, usually described as being heard at the apex. At times it assumes the valvular quality of the second sound. A split first heart sound, usually apical in site, has also been described. Occasionally it will be the second sound which shows this change. None of these altered sounds is characteristic of myocarditis, being readily heard in the presence of fever, anemia, altered metabolic states and in many other types of cardiac abnormalities.

Gallop rhythm may be elicited in the presence of myocarditis even in the absence of clinical heart failure. It is most frequently heard in children who are having a severe bout of rheumatic carditis, but it has also been reported in other types of myocarditis, particularly in patients with Fiedler's (isolated) myocarditis.

Evidence of Cardiac Insufficiency. Occasionally a correct diagnosis of myocarditis has been made in the presence of an acute infection because of the appearance of heart failure in a patient without pre-existing heart disease. This combination of events, especially in children or in young adults, makes the presence of myocarditis likely. Cardiac insufficiency in the presence of recurrent rheumatic carditis is a rather common finding particularly in patients with established valvular deformities, although it is also known to occur during the initial bout of rheumatic fever with carditis.

Progressive myocardial insufficiency, either rapid or gradual, is one of the outstanding clinical features of Fiedler's (isolated) myocarditis.[28] It is common among the late manifestations of the myocarditis associated with subacute bacterial endocarditis. Since the advent of antibiotic therapy it is also encountered in the healing and healed stage of this type of endocarditis, although one author's[29] experience has led him to believe that this form of therapy has decreased the occurrence of heart failure considerably.

It has been said that pulsus alternans probably occurs more often during cardiac insufficiency complicating myocarditis than other myocardial disease. Although an example is

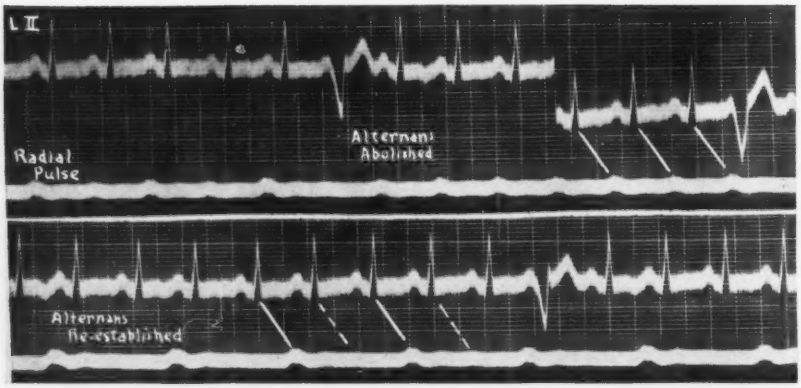

FIG. 1. R. L., white male, 20, with active rheumatic myocarditis and endocarditis with pulsus alternans. The record is continuous and shows electrocardiographic lead II simultaneous with the right radial sphygmogram. At the beginning of the record there is alternation in the size of the pulse beats but not of the electrocardiographic deflections. Toward the middle of the upper strip there is a ventricular premature systole after which the pulsus alternans is abolished. Solid oblique lines connect the electrical with the appropriate mechanical beat. At the end of the strip there is another ventricular premature systole following which (lower strip) the pulsus alternans is re-established (alternating solid and dashed oblique lines). The patient died unexpectedly at home about two months later.

shown in rheumatic myocarditis in figure 1, it is uncommon in our experience. We have seen it most often in the degenerative types of heart disease.

Circulatory collapse or shock is, on occasion, seen in patients with myocarditis and is probably more often peripheral than central in origin. It seems to occur most often in patients with diphtheria. This mechanism may account for the sudden death in these patients. Nevertheless it is well known that unexpected and sudden death is fairly frequent in other types of myocarditis. Among 117 cases of sudden death Lisa[30] found 59 cases of myocarditis, 20 of "infectious" type and 39 of "toxic" type. On the basis of the evidence presented he concluded that infection is a more frequent cause of sudden death than arteriosclerosis. In our 42 cases of myocarditis coming to necropsy at Bellevue Hospital at least four were regarded as having died unexpectedly.

Intracardiac thrombosis is met with in some cases of myocarditis, especially in the Fiedler's type of lesion where heart failure and also embolic phenomena are fairly common. Emboli may be another cause of sudden death even when there is no clinical evidence of active infection.

Fever is a nonspecific finding in many examples of myocarditis and one which may follow any type of pattern. However, there is an appreciable number of cases which show no fever during the course of the disease. This holds true for some of the cases of recurrent or chronic rheumatic carditis which at postmortem are found to have rather extensive signs of inflammation of the myocardium. Fever, therefore, is most apt to be a reflection of the primary disease rather than of the myocarditis, per se.

Leukocytosis. What has been said of fever might be said of leukocytosis, namely, that it is not specific, merely being a response to the primary disease. Many cases of myocarditis, especially the viral and rickettsial types, show no alteration in the total or differential count of white blood cells.

Increased Sedimentation Rate. This laboratory aid seems to be a bit more helpful in establishing a diagnosis of myocarditis than fever and the white blood cell count. There are a significant number of proven examples of myocarditis in which the erythrocytic sedimentation

rate is reported as normal. This is particularly true in the presence of chronic or recurrent rheumatic myocarditis and despite evidence of rather widespread inflammation in the tissues of the heart. The two patients previously described in the Bellevue Hospital series who died following mitral commissurotomy and who at necropsy were found to have rather widespread rheumatic myocarditis had normal sedimentation rates, no fever, and normal white blood cell counts. This negative laboratory information contributed to the erroneous opinion that they were free of active rheumatic infection. It is known that newer nonspecific tests of inflammation, such as the determination of the C-reactive protein, display similar clinical limitations.[31]

If initially elevated, the sedimentation rate may be a helpful guide in determining when a patient with myocarditis may be permitted out of bed.

Although not mentioned among the signs listed in the "Criteria,"[21] hypotension and a small pulse volume have been noted by a number of observers in the course of myocarditis. Hypotension may be seen in those patients even in the absence of heart failure or shock. Possibly it is caused by hyperthermia.

Electrocardiogram

The manifestations of acute myocarditis are often so minor just preceding a serious clinical episode that the electrocardiogram assumes considerable importance as the laboratory aid which may first display suspicious evidence of the lesion. Paradoxically, this aid may also be deceiving if inadequate attention is paid to the many extracardiac variables which can modify it from time to time[32] particularly in the course of a febrile illness. An inspection of many sporadic reports on the electrocardiogram in myocarditis suggests that the changes noted may have been due in some instances to extracardiac causes, or to cardiac causes other than the myocarditis itself.

The "extracardiac causes" which may be encountered in many of the diseases with which myocarditis is associated may be listed as follows: (a) *chemical*, including alkalosis,[33] acidosis,[33] abnormalities of serum electrolytes (particularly potassium and calcium),[34, 35] recent ingestion of a meal with its probable effect on the serum potassium,[36] and hypoxia[37]; (b) *mechanical*, including hypotension as often seen with fever and its consequent effect on the gradient of pressure in the walls of the cardiac chambers, on cardiac position, and on coronary flow especially when shock levels are reached; displacement such as may be caused by pneumonia and effusion; different positions of the patient when recording serial records; (c) *pharmacologic*, such as drugs which may modify the record; and (d) *thermal*, namely hyperpyrexia. A sustained induced temperature of 105 to 107 F. may occasionally cause distinct abnormalities of the T wave in the extremity and precordial leads.[38] Lower temperatures, as produced by intravenous typhoid vaccine, will invariably cause the ventricular gradient, regarded as a vector, to shorten and rotate in a counterclockwise manner both in the frontal plane and in the sagittal plane viewed from the left.[39, 40] This occurs even if the fever is prevented with a simultaneously administered antipyretic.[40] In the electrocardiogram, the change in the magnitude and direction of the gradient manifests itself usually as a lowering of the T wave in lead I and lowering or inversion in leads II, III, and aV_F.

The "cardiac causes" other than myocarditis which may produce electrocardiographic abnormalities include previously existing or progressive valvular deformities or myocardial necrosis. This complicates the interpretation of the record when, for example, inflammation is superimposed on rheumatic valvular, hypertensive, arteriosclerotic, or other types of cardiac disease. Further, there are often diffuse pathologic changes over and above the usual focal inflammatory lesions such as cloudy swelling and fatty infiltration usually regarded as degenerations but considered by some pathologists to be part of the inflammation.[10] The role of these in producing aberrations of the electrical behavior of the heart is uncertain.

The dominant effect of most of these variables is on the labile recovery process represented in the finished record by the S-T segment and the T wave; myocarditis dominantly affects the same process. The consequent need

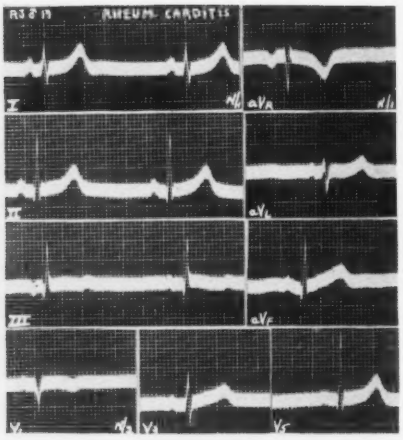

FIG. 2. R. J., white male, 17, with acute rheumatic myocarditis and polyarthritis with sinus bradycardia and prolonged Q-T interval. The bipolar limb leads (I, II, III), the augmented unipolar limb leads (aV_R, aV_L, aV_F), and the precordial leads (V_1, V_3, V_5) were recorded two weeks after the onset of articular pains, and after two days of 120 mg. of corticotropin (ACTH) intramuscularly daily. The heart rate was 43 per minute. Bazett's index was 0.464; the body temperature was normal. Two days before therapy the temperature was 103 F., but the heart displayed a relative bradycardia with a rate of 82 per minute. Time lines occur every 0.04 second. The precordial leads were recorded with the string tension adjusted so that 1 mv. = 0.5 cm. Unless otherwise stated the symbols and technical data are the same in all subsequent electrocardiographic illustrations.

for careful differentiation in interpretation of the records is apparent. A final conclusion on the significance of the electrocardiographic findings will depend, as it always should, on evaluation of them in the light of the total clinical picture.

The incidence of electrocardiographic abnormalities in diseases which can cause myocarditis varies from the rare example of specific myocardial involvement in tuberculosis[41] to almost a 100 per cent incidence in South American trypanosomiasis.[25, 42, 43] Naturally the figure varies with the severity of the primary disease, possibly with the same primary disease caused at different times by pathogens with different degrees of viscerotropism as in poliomyelitis,[6] and with other factors difficult to define or still unknown. The over-all incidence of abnormal electrocardiograms in the course of acute infectious diseases which can cause myocarditis is probably close to 33.3 per cent.[44]

Myocarditis itself may affect rhythmicity, conductivity, and the basic processes of excitation and recovery in both the atria and the ventricles. These effects will manifest themselves in the clinical electrocardiogram as abnormal rhythms and extrasystoles, atrioventricular and intraventricular block, and modifications in the form and duration of the deflections comprising the atrial and ventricular complexes.

Disturbances of rhythm include sinus tachycardia, occasionally atrioventricular nodal rhythm or tachycardia, and premature systoles of various origins. Of fairly common occurrence is a sinus bradycardia in the course of rheumatic carditis (fig. 2). Except in rheumatic myocarditis and an infrequent case of diphtheria,[26] circus rhythm is rare. Ventricular tachycardia has been encountered principally in terminal instances of diphtheritic myocarditis. An example has been described in specific (tuberculous) myocarditis,[41] and we have observed an example of ventricular and bidirectional ventricular tachycardia in the course of acute focal myocarditis of unknown cause (figs. 3 and 4).

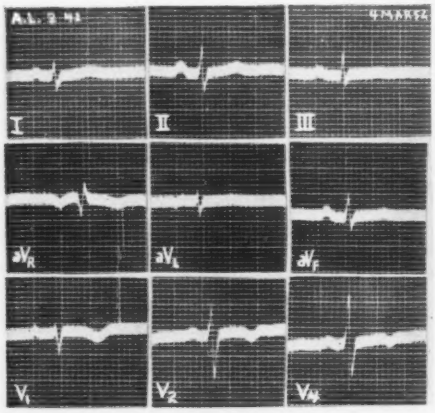

FIG. 3. A. L., Puerto Rican female, 42, with acute focal interstitial myocarditis of unknown cause with some hemorrhage into the epicardial fat. Heart weight 420 Gm. The electrocardiogram was made on March 4, 1952. To be noted are the low voltage of QRS and the inverted T waves in leads V_2 and V_4. The precordial leads were recorded at normal sensitivity (1 mv. = 1 cm.) of the string.

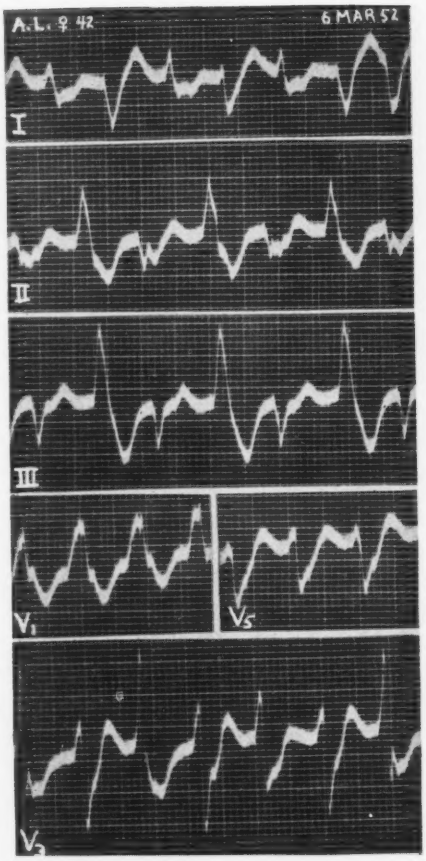

FIG. 4. Electrocardiogram of same patient presented in figure 2 recorded on March 6, 1952, shortly after the onset of a shock-like state. Death occurred two days later. In leads I, II, and III there is a bidirectional ventricular tachycardia; in leads V_1 and V_5 it is an ordinary ventricular tachycardia; in lead V_3 there appears to be a type transitional between the two.

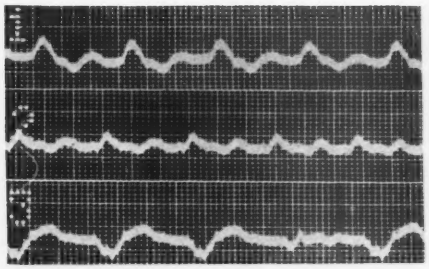

FIG. 5. A. M., white male, 21, with acute isolated (Fiedler's) myocarditis proven at necropsy. This is a reproduction of the first electrocardiogram in acute isolated myocarditis published in 1931 by de la Chapelle and Graef.[28] The standard leads I, II, III disclose a left bundle-branch block with a QRS interval of 0.18 second, a P-R interval at the upper limit of normal (0.20 second), a single ventricular premature systole, and low voltage particularly of the QRS deflections.

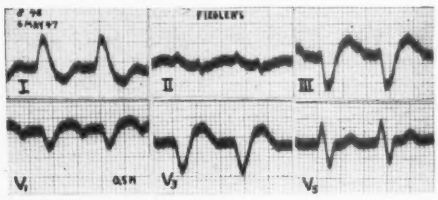

FIG. 6. H. M., white male, 48, with acute isolated (Fiedler's) myocarditis proven at necropsy. The electrocardiogram discloses a left bundle-branch block with a QRS interval of 0.16 second. Several other electrocardiograms showed premature systoles of ventricular origin.

Atrioventricular block occurs characteristically in diphtheritic[5, 8, 23, 45] and in chagasic myocarditis,[25, 42, 43] but may be encountered in lesser grades in other infections and diseases, possibly more frequently in those diseases of actual or suspected viral or rickettsial origin such as poliomyelitis,[46, 47] typhus fever,[48] infectious mononucleosis,[49] and Fiedler's myocarditis.[28] Sporadic examples are reported in other diseases.[50-54] Intraventricular block also occurs most frequently in diphtheria and in Chagas' disease, and in the latter the block almost without exception is of the right bundle branch. Bundle-branch block may be encountered with any diffuse, extensive inflammation such as occurs in Fiedler's myocarditis. The first electrocardiogram published in a case of Fiedler's myocarditis[28] revealed a left bundle-branch block and, at times, incomplete atrioventricular block with ventricular premature systoles (fig. 5). Another example with left bundle-branch block is shown in figure 6. In both of these the block was characterized by a rather wide QRS interval (0.18 and 0.16 second, respectively).

Abnormalities of the P wave have been noted principally when the atrial pacemaker was altered. However, in some instances attention

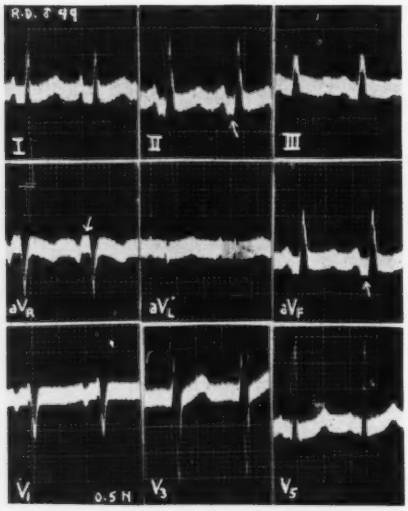

FIG. 7. R. D., white male, 49, with acute bacterial endocarditis (*Streptococcus hemolyticus*) of the aortic valve, abscess of the left atrial wall, and generalized monocytic infiltration of the myocardium. Heart weight, 680 Gm. The electrocardiogram shows a sinus tachycardia with notching of the R wave in leads II, III, and aV_F, a diphasic P wave in lead V_1, and more than usual displacement of the P-R segment (T_P wave) downward in leads II and aV_F, and upward in lead aV_R (arrows).

has been called to high or peaked P waves. No consideration appears to have been given at all to the atrial T wave (T_p). In the electrocardiogram of a 52 year old man with an abscess of the left atrial wall there was distinctive downward displacement of T_p (the P-R segment) seen best in leads II and aV_F with reciprocal elevation in lead aV_R (fig. 7). At necropsy a few days later the heart, which weighed 680 Gm., revealed inflammatory areas in the atrial appendages as well as in the ventricles. There were in addition a gross abscess of the left atrial wall, an acute bacterial (*Streptococcus hemolyticus*) endocarditis of the aortic valve with a mycotic aneurysm of one leaflet and an infarct measuring 1 cm. in diameter in the posterior wall of the left ventricle probably embolic in orgin. The abnormal T_p could be ascribed to atrial suppuration, atrial hypertrophy, or both.

Since the lesions in myocarditis are usually focal and microscopic, modifications of QRS are not usually significant unless there is also intraventricular block, or an extensive destruction of fibers. Unusual notching may occasionally be seen (fig. 7), but to ascribe this to the myocarditis is difficult even when serial records are obtained. Theoretically QRS may be modified much as with infarction if the myocarditis includes a localized abscess in the ventricular muscle. In our experience such a lesion caused by the *Streptococcus viridans* produced no abnormalities of QRS,[55] and the abscess was not suspected until it ruptured through the visceral pericardium causing a purulent pericarditis. Subsequently it spread to include the junctional tissues and caused atrioventricular block.

In a third abscess of the myocardium with two mycotic aneurysms of the interventricular septum, there were no distinctive abnormalities until just before death when the suppurative process ruptured into the myocardium and in so doing severed the right bundle-branch (figs. 8 and 9). The precordial leads displayed deep Q waves in leads V_1 and V_3 (fig. 8) such as are often seen with anteroseptal infarction complicated by right bundle-branch block.

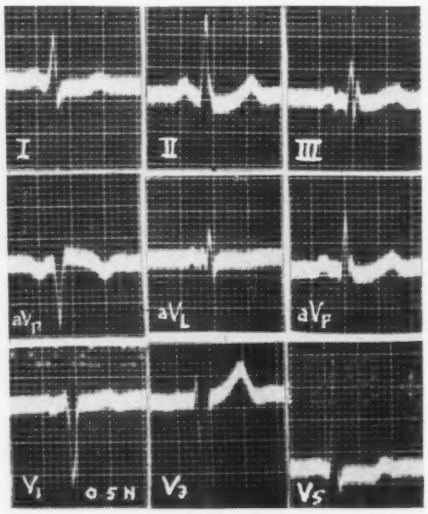

FIG. 8. E. G., white male, 39, with calcific aortic stenosis with acute bacterial endocarditis (*Staphylococcus albus*). The electrocardiogram shows abnormalities of the S-T segment and T wave such as might be caused by left ventricular hypertrophy. The heart weight was 860 Gm. with hypertrophy dominantly of the left ventricle.

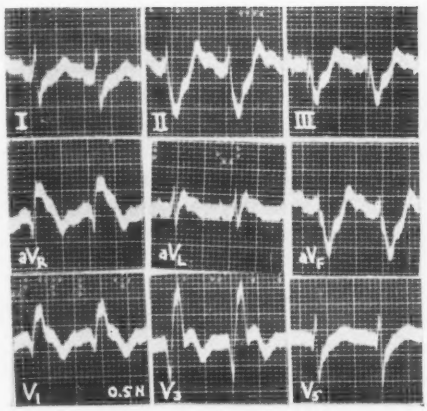

FIG. 9. Electrocardiograms of the same patient presented in figure 8 recorded four days later and six hours after the onset of epigastric and lower substernal pain. There is a right bundle-branch block with deep Q waves in leads V_1 and V_3, and considerable displacement of the S-T junctions in all leads. The patient died six hours later.

In addition to the calcific aortic stenosis, ventricular hypertrophy and acute staphylococcic endocarditis of the aortic valve, there were two mycotic aneurysms approximately 1.5 cm. in diameter at the base of the interventricular septum. One of these extended anterolaterally and actually involved the anterior descending branch of the left coronary artery which, on microscopic section, showed periarteritis but no occlusion. The other aneurysm extended medially through the septum into the anterior right ventricular wall and caused a bulge of the surface of this chamber near the atrioventricular groove. It involved the right coronary artery which also showed inflammatory changes in its walls. Both of the aneurysms were surrounded by necrotic myocardium infiltrated with acute and chronic inflammatory cells, small abscesses and hemorrhage. This acute inflammation of the anterior part of the heart apparently caused the terminal electrocardiographic picture simulating myocardial infarction.

The voltage of the QRS deflections may sometimes be lowered in the type of carditis which progresses to heart failure, or when there is an associated pericardial effusion.

The S-T segment has often been reported to be abnormally elevated or depressed at its origin, or to show an abnormal form in the course of myocarditis. However, neither of these, particularly the displacement, is ever very outstanding with a few notable exceptions.[27, 56] Although not all the causes of change in the form or location of this segment are known, in the light of existing theory displacement of the origin of the segment (S-T junction or J) should not be great in a diffuse myocarditis provided that there is no intraventricular block or unusual hypertrophy. Examination of a good number of the published records as well as our own bears out the theory. Most of them show little or no displacement if measurement is made with the P-R segment as the level of reference. This is the case despite the fact that pathologic correlation will often disclose partially destroyed myocardial fibers where a current of injury might be expected to exist. Even in localized inflammation such as a myocardial abscess or tuberculoma[41] the displacement is not great although it was present in an example of the latter just after a paroxysm of ventricular tachycardia, and in an example of the former just described, when the abscess ruptured into the myocardium.

Nevertheless, serial records in a variety of myocarditides will at times show some change in the positon of the S-T junction and perhaps more often a modification of form. The latter is always associated with a change in the T wave, the most common electrocardiographic abnormality encountered in myocarditis. The change which occurs indicates that the average direction of recovery is altered from normal in different ways. If the new direction of the T wave, regarded as a vector, has a direction backward, upward, and to the left, the clinical record will display lowering of the T wave in lead I, lowering or inversion in leads II and III, and inversion in several or all of the precordial leads, usually on the right half or more of the precordium. This change suggests that the normal ventricular gradient is altered so that recovery is prolonged on the epicardial surface as compared with the endocardial, or at the apex as compared with the base. As noted earlier, fever alone favors this change. If the new direction is forward and to the right and either upward or downward, the T wave characteristically will be inverted in lead I and in left precordial leads (fig. 11).

The duration of abnormality of the S-T segment and T wave varies in different diseases and with different severities of the same disease,

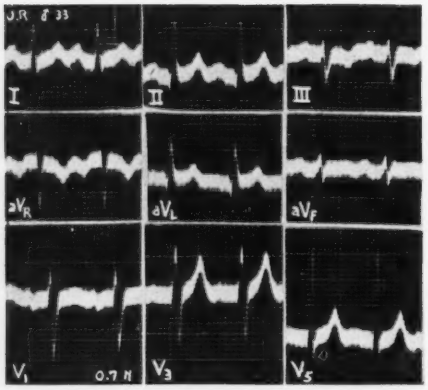

FIG. 10. J. R., white male, 33, with acute bacterial endocarditis of the mitral and tricuspid valves of undetermined cause with acute myocarditis and necrosis. The heart weighed 450 Gm. The record illustrates no definite deviations from normal even though the S-T junction is slightly elevated in leads II and aV_L. The sensitivity of the string when recording the chest leads was 1 mv. = 0.7 cm.

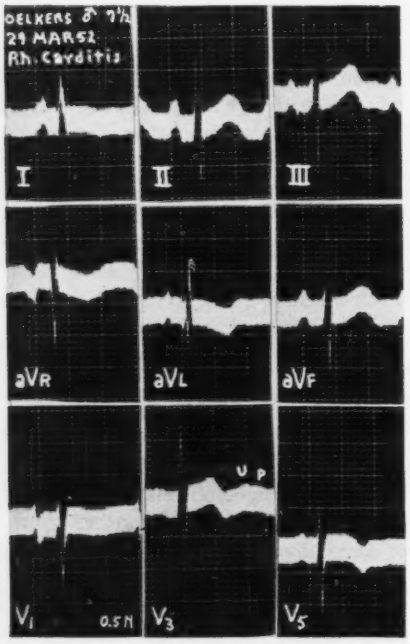

FIG. 11. R. O., white male, 7½, with acute rheumatic carditis and polyarthritis. At the time the electrocardiogram was made the patient had been sick for eight weeks and the day before had received 300 mg. of cortisone by mouth. To be noted is the inversion of the T wave in leads I, aV_L and V_3 with a diphasic T wave and prominent U wave in lead V_3.

but usually evolves over a period of a few days to six weeks if the patient recovers. Naturally this interval may be modified by therapy.

No important changes in the U wave have been described though it is likely that they occur.

Except in rheumatic myocarditis,[57] the Q-T interval has been largely neglected. No measurements seem to have been made of the Q-U interval.

The electrocardiogram may at times be within normal limits when necropsy soon after displays extensive anatomic disease. An example is shown in figure 10. At necropsy a few days later, there was found an acute bacterial endocarditis of unknown cause with diffuse myocarditis. Even though various deflections

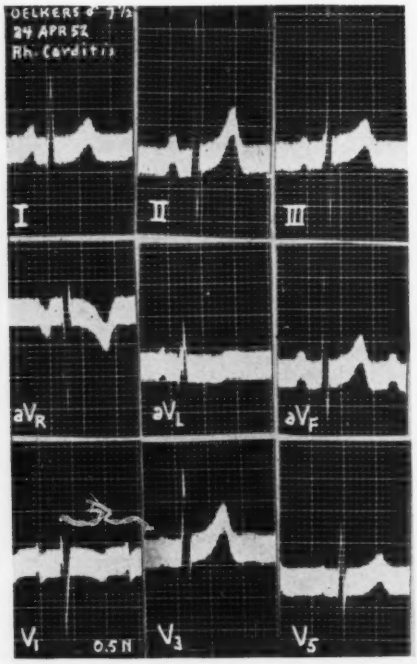

FIG. 12. Electrocardiograms on the same patient presented in figure 11 recorded 26 days later after a course of cortisone of gradually diminishing dosage which at the time of the record was 50 mg. daily. The serum potassium at the time was 3.4 mEq. per liter. All clinical manifestations of rheumatic activity had subsided. Compared with figure 11, the changes in the direction and form of the T waves are to be noted, particularly the high, pointed T wave in lead II, which is not an uncommon finding usually in the convalescent stage of rheumatic myocarditis.

are not beyond normal quantitatively, qualitative changes may often be suggestive. Of fairly frequent occurrence in this regard is the development of high, peaked T waves in the healing stage of rheumatic carditis (figs. 11 and 12).

Prognosis

There is very little that can be said regarding the prognosis of myocarditis since so few cases are recognized at the bedside, excluding those of specific type such as the rheumatic. It seems desirable, therefore, to consider the prognosis of myocarditis in relation to the disease of which it is a complication or a manifestation. There is a group, however, usually classified as Fiedler's (isolated) myocarditis which does not seem related to any particular disease.

In the latter group, that is, Fiedler's myocarditis, the prognosis, both immediate and ultimate, is poor. These patients are prone to many complications such as embolic phenomena, serious conduction defects and, most important, progressive and rather rapid heart failure. Occasionally death is rather sudden or unexpected. The usual cardiac therapy does not seem to alter the prognosis of these cases even in those instances where the correct diagnosis was made early in the course of the disease. However, the new hormones such as corticotropin (ACTH) and cortisone may be found to be effective in these cases. One case report is already at hand indicating that corticotropin therapy proved beneficial in curing a 7 year old boy with myocarditis of undetermined etiology simulating Fiedler's type.[58]

It is conceivable that some of the myocarditides which occur in the presence of acute and subacute bacterial endocarditis may react favorably to the antibiotic therapy now being used routinely in such cases. Certainly the prognosis of these bacterial forms of endocarditis has become distinctly favorable since the use of the antibiotics. Unfortunately two adverse features of antibiotic therapy have made their appearance in recent years: (1) an increase in penicillin-resistant bacteria,[59] especially among strains of Staphylococci and slightly less so among the Streptococci which cause endocarditis; (2) the rather frequent occurrence of heart failure, commonly progressing to death, in patients in whom the endocarditis has been "cured" by antibiotic therapy.[60] Most of the latter patients have a complicating myocarditis of rather extensive nature and which does not respond as well to the antibiotics as the endocardial lesions.

The prognosis of rheumatic myocarditis is dependent on the prognosis of the primary disease, namely rheumatic fever. Its mortality from the acute attack varies between 1 and 4 per cent and is practically always due to acute carditis.[61] However, the highest mortality rate in children with rheumatic heart disease occurs during a period of three to five years after the initial attack of rheumatic fever.[62] During this interval, carditis is an important, if not the most important, factor in causing death. In about 80 per cent of all cases, the cause of death in children with rheumatic heart disease is rheumatic fever and carditis, the latter including myocarditis. As seen in the nine instances of rheumatic heart disease coming to necropsy in the Bellevue Hospital group myocarditis may also occur in adult life. All nine cases were adults ranging from 19 to 64 years. The majority died of congestive heart failure, and it seems likely that the underlying myocarditis was at least a contributory factor to the heart failure as well as to death.

Possibly the prognosis of rheumatic myocarditis is already being influenced by the increasing use of hormone therapy including cortisone and corticotropin. The preliminary report issued in June 1952 by the Cooperative Rheumatic Fever Study[63] stated: "In the type of cases admitted to the trial and with the regime of treatment laid down, it appears that individual symptoms, signs or laboratory observations may have been affected more favorably by one or another of these three drugs, but no consistent pattern is evident. In short, no firm conclusions can at present be drawn concerning the drug most effective in the control of the acute illness. The cases have not been under observation sufficiently long to provide data on the prevention of rheumatic heart disease." The three drugs used in the study were cortisone, corticotropin and acetylsalicylic acid. Other reports have been appearing more recently suggesting rather striking

results by the use of the hormones but with larger doses than those employed in the cooperative study. Wilson and her co-workers[64] imply that the short-term administration of corticotropin modifies the natural course of active rheumatic carditis with respect to severity, duration and absence of overt clinical evidence of residual cardiac damage.

Diphtheritic myocarditis must always be given a poor prognosis even though a number of patients survive this very serious complication of diphtheria, regardless of whether the site of initial infection is in the nose or throat or in the skin. The fatality rate from myocarditis seems to be highest in the later phase of the disease including the convalescent period, but unexpected circulatory or cardiac failure as well as sudden death may occur during any part of the clinical course. In one-third of a large series of cases reviewed by Gore[5] the manifestations of myocarditis appeared at a time when the patient seemed to be well on his way to convalescence. He states that the interval between diphtheria and the onset of cardiac symptoms has been designated as the "deceptive interval of apparent improvement." Early clinical diagnosis of the primary disease and early administration of adequate amounts of antitoxin undoubtedly help in preventing myocarditis and thereby lessen the mortality. Long periods of convalescence sufficient to heal the myocardial process may also reduce the mortality rate even though the residual damage of the myocardium which some cases may show will not necessarily be prevented.

It would seem the part of wisdom to give all patients with myocarditis occurring in various infectious diseases sufficient rest in bed to permit the myocardial inflammatory process to pass into a healed stage as determined clinically and electrocardiographically.

Treatment

Among the many diseases which may cause myocarditis there are some which can be prevented. Among these are rheumatic fever and diphtheria. The latter can be prevented by proper immunization measures. Rheumatic fever can be prevented to a great extent by routinely treating all infections of the upper respiratory tract, especially tonsillitis and pharyngitis, with appropriate and intensive antibiotic therapy. In children and young adults who already have rheumatic heart disease, the prophylactic use of sulfadiazine will reduce the rate of recurrent rheumatic fever and carditis.[61, 65] Experience with the use of long-acting antibiotics over the past few years is also very encouraging in the prevention of recurrent rheumatic fever.[61, 66]

Bacterial endocarditis can be prevented by the prophylactic use of chemotherapy in any patient known to have congenital or acquired heart disease for one day prior to, and for 48 hours after, operative procedures such as extraction of a tooth, tonsillectomy, and after childbirth. Correction of sepsis or pyemia by intensive antibacterial therapy in conjunction with appropriate surgical procedures or by the use of therapeutic enzymes (streptodornase-streptokinase) will prevent the occurrence of bacterial endocarditis and probably myocarditis too.

In the management of diphtheritic myocarditis, the importance of early recognition of the primary disease as well as the early administration of adequate amounts of antitoxin should be given major emphasis. It is well to keep in mind the so-called "deceptive interval of improvement" which has been observed so often prior to the onset of cardiac complications.[5] Since the manifestations of myocarditis may occur late in the course of the disease, convalescence should be prolonged in order to allow healing of the myocardial damage with subsequent reduction in the number of sudden or unexpected deaths.

The management of rheumatic myocarditis will usually include the use of salicylates, cortisone, or corticotropin. As previously quoted, the Cooperative Rheumatic Fever Study[8] in its preliminary report concerning the relative merits of these three drugs was unable to draw any firm conclusions as to which was most effective in the control of rheumatic fever. Needless to say these conclusions do not permit one to make a definitive choice among these three therapeutic agents. However, reports are beginning to appear intimating the superiority of the hormones and their effectiveness in

controlling the acute manifestations of rheumatic fever including carditis and in reducing the incidence or severity of sequelae.[64] Perhaps with increasing experience and modification of dosage, the hormones will assume an important role in the treatment of rheumatic carditis and possibly in the prevention of structural deformities.

Regardless of which medicines are used, bed rest and supportive measures are indicated until clinical manifestations and electrocardiographic records indicate that the myocardial inflammatory process has become quiescent. If heart failure, arrhythmia, or other circulatory complications should intervene, they must be handled in the same manner as in other types of heart disease.

As an important preventive of myocarditis, the therapy of acute and subacute bacterial endocarditis should not be delayed. Antibiotic therapy, preferably beginning with penicillin, should be started within 48 hours after the diagnosis of bacterial endocarditis has been made, only withholding the drug long enough to obtain blood for culture.[67] Subsequently, depending on the in vitro characteristics of the microorganism and the clinical response, the most effective antibiotic or combination of antibiotics should be employed. If signs of heart failure intervene, the therapy should include the measures usually outlined, such as restricted sodium intake, digitalization, diuretics if needed, continued bed rest and correction of anemia if present. Any arrhythmia which may arise must also be treated by the necessary therapeutic agents to prevent heart failure or embolic complications.

Therapy of isolated (Fiedler's) myocarditis consists mainly of the treatment of the congestive heart failure which these patients so frequently present. In view of the rather high incidence of thromboembolic complications, anticoagulant therapy should be seriously considered. Cortisone and corticotropin may lead to recovery, at least temporarily, of some of these cases as suggested earlier.[58] Since there is always a possibility that some instances of Fiedler's myocarditis may have a bacterial or viral origin, the use of antibiotics should also be considered.

The treatment of that form of myocarditis considered to be "allergic" or associated with hypersensitivity, for example, to sulfonamides, antibiotics or biologic sera, should include the use of antihistamines,[68] and possibly the corticosteroids.[69]

In the management of patients with myocarditis secondary to parasitic infestation, the parasiticide indicated for the specific causative agent should be employed. As manifestations of myocardial involvement appear, the necessary measures to control them must be instituted. Similar considerations apply to the management of the myocarditides occurring in the presence of rickettsial and viral diseases.

Summary

A review of selected papers on myocarditis published during the past decade and an analysis of some original data together with personal experiences have been presented.

All of these indicate that the clinical diagnosis of myocarditis is made far too infrequently as contrasted with the high incidence of this disease as recognized by pathologists. It is estimated that approximately 10 per cent of all patients coming to necropsy will demonstrate some evidence of myocarditis.

The discrepancy between the clinical and the pathologic incidences can possibly be ascribed to two factors, namely, (a) the relatively innocent nature of the clinical and laboratory findings in many cases, and (b) the apparent reluctance of the clinician to make the diagnosis.

It is likely that a correct diagnosis of myocarditis will be made more often and cardiac catastrophies avoided if the clinician will consider the possibility of the diagnosis, particularly in the course of all types of infectious diseases.

Acknowledgments

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REFERENCES

[1] SAPHIR, O.: Nonrheumatic inflammatory diseases of the heart, C. Myocarditis. In Gould, S. E.: Pathology of the Heart, ed. 1. Springfield, Ill., Charles C Thomas, 1953. Pp. 784–835.

[2] GORE, I., AND SAPHIR, O.: Myocarditis. A classification of 1402 cases. Am. Heart J. **34:** 827, 1947.

[3] MORITZ, A. R., AND ZAMCHECK, N.: Sudden and unexpected deaths of young soldiers. Arch. Path. **42:** 459, 1946.

[4] KUSCHNER, M., AND LEVIEFF, L.: Correlation between active rheumatic lesions in the left auricular appendage and elsewhere in the heart. Am. J. M. Sc. **226:** 290, 1953.

[5] GORE, I.: Myocardial changes in fatal diphtheria. A summary of observations in 221 cases. Am. J. M. Sc. **215:** 257, 1948.

[6] TELOH, H. A.: Myocarditis in poliomyelitis. Arch. Path. **55:** 408, 1953.

[7] DOLGOPOL, V. B., AND CRAGAN, M. D.: Myocardial changes in poliomyelitis. Arch. Path. **46:** 202, 1948.

[8] BURKHARDT, E. A., EGGLESTON, C., AND SMITH, L. W.: Electrocardiographic changes and peripheral nerve palsies in toxic diphtheria. Am. J. M. Sc. **195:** 301, 1938.

[9] SAPHIR, O.: Myocarditis, a general review with analysis of 240 cases. Arch. Path. **32:** 1000, 1941; **33:** 88, 1942.

[10] KARSNER, H. T.: Human Pathology, ed. 6. Philadelphia, Lippincott, 1942. P. 372.

[11] WELLS, A. H., AND SAX, S. G.: Isolated myocarditis probably of sulfonamide origin. Am. Heart J. **30:** 522, 1945.

[12] FAWCETT, R. M.: Myocardium after sulfonamide therapy. Arch. Path. **45:** 25, 1948.

[13] FRENCH, A. J., AND WELLER, C. V.: Interstitial myocarditis following the clinical and experimental use of sulfonamide drugs. Am. J. Path. **18:** 109, 1942.

[14] SAPHIR, O.: Virus myocarditis. Mod. Concepts Cardiovas. Dis. **6:** 43, 1949.

[15] JUNGEBLUT, C. W., AND EDWARDS, J. E.: Isolation of poliomyelitis virus from the heart in fatal cases. Am. J. Clin. Path. **21:** 601, 1951.

[16] HELWIG, F. C., AND SCHMIDT, E. C. H.: A filter-passing agent producing interstitial myocarditis in anthropoid apes and small animals. Science **102:** 31, 1945.

[17] SCHMIDT, E. C. H.: Virus myocarditis. Pathologic and experimental studies. Am. J. Path. **24:** 97, 1948.

[18] WARREN, J., AND SMADEL, J. E.: Further observations on the virus of encephalomyocarditis. J. Bact. **51:** 615, 1946.

[19] SAPHIR, O.: Encephalomyocarditis. Circulation **6:** 843, 1952.

[20] FRIEDBERG, C. K.: Diseases of the Heart. Philadelphia, Saunders, 1949. P. 542.

[21] Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels, ed. 5. New York. New York Heart Association, 1953. P. 65.

[22] HIRSCH, J. G., AND FLETT, D. M.: Sinus bradycardia in acute rheumatic fever. Ann. Int. Med. **36:** 146, 1952.

[23] ALTSCHULER, S. S., HOFFMAN, K. M., AND FITZGERALD, P. J.: Electrocardiographic changes in diphtheria. Ann. Int. Med. **29:** 294, 1948.

[24] LOGUE, R. B., AND HAUSER, J. F.: Heart block. A study of 100 cases with prolonged P-R interval. Am. J. M. Sc. **207:** 867, 1944.

[25] PERA, J. S.: O electrocardiograma na cardiopatia chagasica crônica. Arq. brasil cardiol. **5:** 427, 1952.

[26] NEUBAUER, C.: Auricular fibrillation and auricular flutter in diphtheria. Brit. Heart J. **7:** 59, 1945.

[27] COOKSON, H.: Heart block and the simulation of bundle block in diphtheria. Brit. Heart J. **7:** 63, 1945.

[28] DE LA CHAPELLE, C. E., AND GRAEF, I.: Acute isolated myocarditis with report of a case. Arch. Int. Med. **47:** 942, 1931.

[29] FIESE, M. J.: Cardiac failure in penicillin-treated subacute bacterial endocarditis. Arch. Int. Med. **79:** 436, 1947.

[30] LISA, J. R., AND HART, J. F.: The role of infection in sudden death. New York J. Med. **40:** 705, 1940.

[31] STOLLERMAN, G. H., GLICK, S., PATEL, D. J., HIRSCHFELD, I., AND RUSOFF, J. H.: Determination of C-reactive protein in serum as a guide to the treatment and management of rheumatic fever. Am. J. Med. **15:** 645, 1953.

[32] KOSSMANN, C. E.: The normal electrocardiogram. Circulation **8:** 920, 1953.

[33] BAKER, P. S., SHRADER, E. L., AND RONZONI, E.: The effects of alkalosis and acidosis upon the human electrocardiogram. Am. Heart J. **17:** 169, 1939.

[34] SURAWICZ, B., AND LEPESCHKIN, E.: The electrocardiographic pattern of hypopotassemia with and without hypocalcemia. Circulation **8:** 801, 1953.

[35] BAKER, P. S., JOHNSTON, F. D., AND WILSON, F. N.: The duration of systole in hypocalcemia. Am. Heart J. **14:** 82, 1937.

[36] SIMONSON, E., AND KEYS, A.: The effect of an ordinary meal on the electrocardiogram. Normal standards in middle-aged men and women. Circulation **1:** 1000, 1950.

[37] WHITE, M. S.: The effect of anoxia in high altitude flights on the electrocardiogram. J. Aviation Med. **11:** 166, 1950.

[38] CLAGETT, A. H.: The electrocardiographic changes following artificial hyperpyrexia. Am. J. M. Sc. **208:** 81, 1944.

[39] FREEDBERG, A. S., MCMANUS, M. J., AND ALTSCHULE, M. D.: The electrocardiogram in man during an episode of chill and fever induced by intravenous typhoid vaccine. Am. Heart J. **34:** 249, 1947.

[40] BRUMLÍK, J., AND KOSSMANN, C. E.: Frontal and sagittal electrocardiograms of normal and hypertensive subjects during an experimentally produced phase of lowered blood pressure. Circulation **5:** 712, 1952.

[41] SCHNITZER, R.: Myocardial tuberculosis with paroxysmal ventricular tachycardia. Brit. Heart J. **9:** 213, 1947.

[42] DIOS, E., LARANJA, F. S., AND NOBREGA, G.: Doença de Chagas. Mem. Inst. Oswaldo Cruz **43:** 495, 1945.

[43] PONDÉ, A. DE A., AND COLLABORATORS: A Doença de Chagas na Bahia. Arq. Univ. Bahia Fac. med. **1:** 333, 1946.

[44] FINE, I., BRAINERD, H., AND SOKOLOW, M.: Myocarditis in acute infectious diseases. A clinical and electrocardiographic study. Circulation **2:** 859, 1950.

[45] KAY, C., AND LIVINGOOD, C. S.: Myocardial complications of cutaneous diphtheria. Am. Heart J. **31:** 744, 1946.

[46] BRANDFORD, H. A., AND ANDERSON, L. L.: Electrocardiographic observations during a poliomyelitis epidemic. Ann. Int. Med. **32:** 270, 1950.

[47] GEFTER, W. I., LEAMAN, JR., W. G., LUCCHESI, P. F., MAHER, I. E., AND DWORIN, M.: The heart in acute anterior poliomyelitis. Am. Heart J. **33:** 228, 1947.

[48] CIMMINO, V.: Myocardial damage in typhus fever studied by electrocardiograph. Trop. Dis. Bull. **41:** 26, 1944.

[49] WECHSLER, H. F., ROSENBLUM, A. H., AND SILLS, C. T.: Infectious mononucleosis; report of an epidemic in an Army post. Part II. Ann. Int. Med. **25:** 236, 1946.

[50] HALL, W. H., AND FINEGOLD, S.: A study of 23 cases of Reiter's syndrome. Ann. Int. Med. **38:** 533, 1953.

[51] MAINZER, F.: Electrocardiographic study of typhoid myocarditis. Brit. Heart J. **9:** 145, 1947.

[52] ABT, A. F., AND VINNECOUR, M. I.: Electrocardiographic studies during pneumonia in infants and children. Am. J. Dis. Child. **47:** 737, 1934.

[53] CANDEL, S., AND WHEELOCK, M. C.: Acute nonspecific myocarditis. Ann. Int. Med. **23:** 309, 1945.

[54] HOLLANDER, G.: Electrocardiographic changes in scrub typhus fever. Am. Heart J. **31:** 481, 1946.

[55] BERGER, A. R., AND KOSSMANN, C. E.: Solitary myocardial abscess in subacute bacterial endocarditis. Ann. Int. Med. **35:** 1125, 1951.

[56] SHEARER, M. C.: "Plateau R-T" in a case of lobar pneumonia. Am. Heart J. **5:** 801, 1930.

[57] CRAIGE, E., ALIMURUNG, M. M., BLAND, E. F., AND MASSELL, B. F.: The Q-T interval in rheumatic fever. Circulation **1:** 1338, 1950.

[58] GARRISON, R. F., AND SWISHER, R. C.: Myocarditis of unknown etiology (Fiedler's) treated with ACTH; report of a case in a 7 year old boy with improvement. J. Pediat. **42:** 591, 1953.

[59] EDITORIAL. Bacterial versatility. Ann. Int. Med. **36:** 196, 1952.

[60] CORRELL, H. L., LUBITZ, J. M., AND LINDERT, M. C. F.: Bacterial endocarditis: clinico-pathologic studies of untreated, treated and cured patients. Ann. Int. Med. **35:** 45, 1951.

[61] SWIFT, H. F.: Rheumatic fever. In Cecil and Loeb: A Textbook of Medicine, ed. 8. Philadelphia, Saunders, 1951. P. 163.

[62] DE LA CHAPELLE, C. E.: Rheumatic heart disease. In Cecil & Loeb: A Textbook of Medicine, ed. 8. Philadelphia, Saunders, 1951. P. 1103.

[63] A preliminary statement on the Cooperative Rheumatic Fever Study. The use of ACTH and cortisone in the treatment of rheumatic fever. Circulation **6:** 317, 1952.

[64] WILSON, M. G., HELPER, H. N., LUBSCHEZ, R., HAIN, K., AND EPSTEIN, N.: Effect of short-term administration of corticotropin in active rheumatic carditis. J. Dis. Child. **86:** 131, 1953.

[65] KUTTNER, A. G., AND REYERSBACK, G.: The prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide. J. Clin. Investigation **22:** 77, 1943.

[66] KUTTNER, A. G.: Prevention of rheumatic fever and rheumatic heart disease. Postgrad. Med. **14:** 429, 1953.

[67] FINLAND, M.: Treatment of bacterial endocarditis. Circulation **9:** 292, 1954.

[68] MORITZ, E.: Die behandlung der allergischen serösen myokarditis (myokardose) mit Antihistaminpräparaten. Wien. Med. Wchnschr. **101:** 791, 1951.

[69] NEUSTADT, D. H.: Transient electrocardiographic changes simulating an acute myocarditis in serum sickness. Ann. Int. Med. **39:** 126, 1953.

CLINICAL CONFERENCES

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Myxoma of the Left Atrium Simulating Mitral Stenosis

By JOHN W. HARRISON, M.D., LAWRENCE J. MCCORMACK, M.D., AND A. CARLTON ERNSTENE, M.D.

MYXOMA of the left atrium, although of rare occurrence, is the most common form of primary tumor of the heart.[1] In the past, its recognition was a matter of academic interest only, but with the development of intracardiac surgery, its detection has become of practical importance. In the first place, the tumor may cause auscultatory and hemodynamic changes that may lead to an erroneous diagnosis of mitral stenosis. Second, myxomas of the atrium usually are pedunculated, and their surgical removal should be possible. The present case is reported to emphasize these two points and to direct attention to certain clinical features of atrial tumors that may aid in their diagnosis.

ABSTRACT OF CASE

A white, married woman, aged 50 years, was admitted to the Cleveland Clinic Hospital on March 14, 1953, because of dyspnea, orthopnea, cough, abdominal discomfort, nausea and occasional vomiting. Shortness of breath on exertion, fatigue and weakness had first been noted approximately nine months earlier. These symptoms had become progressively worse, and for three months prior to entering the hospital there had been orthopnea and a persistent cough productive at times of pink-tinged frothy sputum. On two occasions the patient had been awakened in the early morning hours by severe paroxysmal dyspnea. Nausea and occasional vomiting had developed in January, 1953, following treatment with digitoxin and a low-sodium diet and, because of the persistence of these symptoms, all therapy had been discontinued two weeks before admission. Edema of the ankles first was noted two days before entering the hospital. There had been a gradual loss of 14 pounds in weight since the onset of the illness.

The past medical history did not contribute significant information. There had been no illness suggestive of rheumatic fever, and the patient never had been informed of the presence of a heart murmur.

Physical examination revealed a well-developed and fairly well-nourished woman in no respiratory distress when well propped up in bed. The temperature was normal, the heart rate 100 per minute, and the blood pressure 100 mm. Hg systolic and 70 mm. diastolic. The veins of the neck were moderately distended, but there was no cyanosis and no malar flush. The area of relative cardiac dullness extended 11 cm. from the midsternal line in the fifth intercostal space. The heart rhythm was regular except for occasional premature beats. The first sound at the apex and the second sound at the pulmonary area were accentuated. The initial examiner reported the presence of a grade 2 late diastolic apical murmur with a presystolic crescendo. The lungs were clear on percussion, but on auscultation a moderate number of medium moist rales could be heard over the right base posteriorly. The liver extended 4 cm. below the costal margin in the right midclavicular line and was slightly tender. There was no peripheral edema.

On the morning following admission, the patient was examined by several members of the medical staff, including the original examiner, and none could confirm the presence of a mitral diastolic murmur, even with the patient lying in the left lateral position. Four days later, however, one examiner again detected the murmur.

The urinalysis and blood count gave normal findings, and the Wassermann reaction of the blood was negative.

An electrocardiogram showed sinus tachycardia with a rate of 110 per minute and changes in the precordial leads indicative of right ventricular hypertrophy.

Fluoroscopic and roentgenographic studies of the thorax revealed a moderate increase in the size of the heart, the enlargement involving predominantly the outflow tract of the right ventricle (fig. 1). Studies in the oblique positions showed slight enlargement of the right atrium but only questionable enlargement of the left atrium. The left ventricle appeared to be of normal size, and no valvular calcifications could be seen. The hilar vessels were prominent bilaterally but did not pulsate.

Treatment with digitalis, a low-sodium diet, and mercurial diuretics resulted in prompt improvement,

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and on the fourth day Dr. F. Mason Sones, Jr., performed cardiac catheterization. The results of the studies are presented in the table.

The patient continued to improve, but on several occasions she experienced sudden spells of nausea, colicky pain in the upper abdomen, and an abrupt return of severe dyspnea, tachypnea, and orthopnea.

DR. HARRISON: On the basis of the clinical, roentgenographic and electrocardiographic observations, a diagnosis of rheumatic heart disease with severe mitral stenosis appeared to be justified. The fact that a diastolic apical murmur was detected on only two or three occasions and never was heard simultaneously by two or more observers was a disturbing feature. The elevated pulmonary artery and pulmonary "capillary" pressure, however, indicated a high resistance to blood flow beyond the pulmonary arteriolar bed, and this was considered further evidence in favor of the presence of mitral stenosis. The pulmonary arteriolar resistance and the total pulmonary resistance at rest were about four times that normally encountered. It was presumed that the orifice of the mitral valve was so greatly reduced that a diastolic murmur either was not produced or occurred only inconstantly.

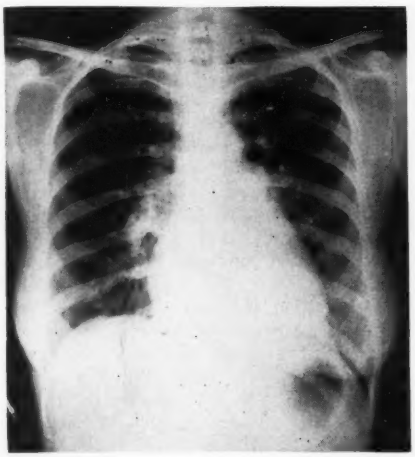

FIG. 1. Roentgenogram of the thorax demonstrating enlargement of the outflow tract of the right ventricle.

DR. ERNSTENE: I believe that that was a reasonable assumption. The murmur of mitral stenosis is difficult to hear in certain patients, and the ease with which it is detected may vary from time to time. Differences in the heart rate are responsible for some of these fluctuations, but I suspect that variation in the auditory acuity of the examiner also is an important factor. At times the murmur of mitral stenosis may be detectable only after exercise or with the patient lying in the left lateral position, but neither of these maneuvers was of help in the present instance. It has been emphasized repeatedly, chiefly with reference to the murmur of mitral insufficiency and some of the congenital cardiac anomalies, that no parallelism exists between the intensity of a murmur and the size of the aperture through which the blood is flowing. Either a very small or a very large defect may fail to produce a bruit.

The first sound at the apex and the pulmonary second sound were accentuated. These findings are, of course, consistent with the presence of mitral stenosis. No "opening snap" of the mitral valve was heard at any time.

TABLE 1.—*Results of Cardiac Catheterization Studies*

	Rest	Exercise
Oxygen capacity of blood	15.3 vol. %	—
Oxygen content of arterial blood	13.6 vol. %	13.3 vol. %
Oxygen content of pulmonary "capillary" blood	14.8 vol. %	14.0 vol. %
Oxygen content of pulmonary artery blood	9.0 vol. %	5.2 vol. %
Cardiac output	5.35 L./min.	3.82 L./min.
Cardiac index	3.57 L./min./M.^{2}	2.57 L./min./M.^{2}
Mean pulmonary artery pressure	91/41 (62) mm. Hg	88/43 (63) mm. Hg
Mean pulmonary "capillary" pressure	26 mm. Hg	
Right ventricular pressure	88/9 mm. Hg	
Mean right auricular pressure	7 mm. Hg	
Pulmonary arteriolar resistance	384 dynes/sec./cm.$^{-5}$	
Total pulmonary resistance	920 dynes/sec./cm.$^{-5}$	

One roentgenologic feature was present that should have called for caution in accepting the diagnosis of mitral stenosis, namely, the fact that only slight or questionable enlargement of the left atrium could be demonstrated. If severe mitral stenosis were responsible for the patient's congestive failure, the valvular lesion should have been present for a long time and ordinarily would have produced considerable enlargement of the atrium. I should like to ask Dr. Harrison how severe the congestive failure was and whether or not the possibility of primary pulmonary disease was considered as a cause of illness.

DR. HARRISON: At the time of the patient's admission, orthopnea was present; the jugular veins were engorged even with the patient sitting erect; there were rales over the base of the right lung; and the liver was large and tender. Furthermore, there was a loss of 16 pounds in weight during the first seven days in the hospital, after which the weight remained stationary.

With regard to the question of primary lung disease, roentgenographic examination of the chest showed no evidence of any such condition. Complete pulmonary function studies were made and revealed a 20 per cent reduction in the vital capacity of the lungs, a normal residual air space, moderate reduction in total lung volume, normal maximum breathing capacity, and hyperventilation at rest. These findings were interpreted as being consistent with mild pulmonary fibrosis or pulmonary congestion, and in view of the clinical response to treatment it was believed that the latter explanation was the correct one.

DR. ERNSTENE: In the daily progress notes several episodes are described in which there was an abrupt return of dyspnea and orthopnea accompanied by nausea and abdominal pain. What was the cause of those spells?

DR. HARRISON: No adequate explanation was offered. It was believed that acute left ventricular failure could be excluded in view of the fact that the left ventricle was not enlarged and the attacks continued to recur even after the patient's condition otherwise was much improved. The paroxysms occurred without detectable precipitating factors and were not accompanied by an increase in the number of rales in the lungs or by more than a moderate rise in the heart rate. Because the patient invariably became upset and anxious, the possibility was considered that the respiratory distress was part of an emotional reaction to abdominal pain. However, roentgenographic studies of the gallbladder and upper gastrointestinal tract revealed no abnormalities, and repeated measurements of the serum amylase also were normal. The liver did not seem to increase in size or become more tender during the attacks.

DR. ERNSTENE: Will you continue with the clinical history? It appears that everyone who examined the patient ultimately accepted the diagnosis of mitral stenosis.

DR. HARRISON: The diagnosis was considered established and mitral commissurotomy was advised. The patient, however, requested a temporary postponement, and because her condition had improved satisfactorily, she was allowed to return home for one month. Three weeks after leaving the hospital she was readmitted because of a sudden return of dyspnea and orthopnea, cough productive of blood-tinged sputum, pain in the right flank and right upper abdomen, and abdominal distention. There had been repeated vomiting. The body weight had not increased.

On examination, the patient appeared acutely ill. There was great respiratory distress, the neck veins were distended, and the skin was pale, cool, and clammy. Cyanosis was not noted. The heart rate was 104 per minute, and the blood pressure 70 mm. Hg systolic and 40 mm. diastolic. There were no cardiac murmurs. A few coarse moist rales were present over the base of the right lung. The liver extended 5 cm. below the costal margin in the right midclavicular line and was very tender. There was minimal edema about both ankles. A diagnosis of pulmonary infarction was made. On the following day, icterus was noted for the first time. The blood urea content was 87 mg. per 100 cc. Roentgenograms of the chest showed an irregular area of increased density in the lower lobe of the right lung, approximately 4 cm. in diameter.

The patient's condition deteriorated gradually but steadily. Rales appeared in increasing number; dyspnea and orthopnea persisted; abdominal distention increased; the edema of the legs became more marked; and there was progressively severe prostration. Periods of confusion and stupor developed and deepened gradually to terminal coma. The arms and legs remained cold and pale, and tachycardia and hypotension persisted. Death occurred on the ninth day after admission.

DR. ERNSTENE: Was pulmonary infarction considered to be the principal factor responsible for the terminal course of events?

DR. HARRISON: No. The area of infarction did not seem large enough for that. The primary cause was considered to be a change in the condition of the heart. The appearance of the patient and the clinical course raised increasing doubt in the minds of several consultants that the primary cardiac problem was mitral stenosis. No positive diagnosis was offered, but in discussing the problem the possibilities of ball-valve thrombus and tumor of the left atrium were mentioned. The first of these conditions was not considered likely because occluding thrombi of the left atrium usually are associated with mitral stenosis and/or auricular fibrillation. In this case, the presence of mitral stenosis appeared increasingly doubtful, and the heart rhythm remained regular throughout the illness. The persistent hypotension, tachycardia, and coldness of the extremities were, of course, compatible with high-grade occlusion of the mitral orifice by a thrombus. The possibility of a left atrial tumor was not considered beyond the point of passing comment.

I should like to ask Dr. McCormack to present the postmortem findings.

DR. MCCORMACK: The pertinent necropsy findings were observed in the heart, lungs, liver, and adrenal glands.

The *heart* was symmetrically enlarged and weighed 350 Gm. No localized chamber enlargement was present. The epicardial surface was normal. The coronary arteries were normal. The myocardium was firm and reddish tan in color. The right ventricle measured 0.7 cm. and the left 1.2 cm. in thickness, signifying some muscular hypertrophy. The leaflets of all valves were entirely normal, and there were no scarring, thickening, or shortening of the chordae tendineae.

Within the left atrium, a rubbery, slightly lobulated mass was firmly attached by a short pedicle to the interatrial septum in the region of the posterior portion of the valve of the fossa ovalis (fig. 2). The tumor was mottled red, gray, and yellow and measured 5.0 cm. in length and 4.0 cm. in diameter. The pedicle was 1.5 cm. in diameter. On cross section, the mass was homogeneous, gray, and translucent.

Microscopically, the tumor possessed a uniform appearance and presented as its outstanding feature a large number of blood vessels of capillary size coursing through the lesion (fig. 3). Areas of focal

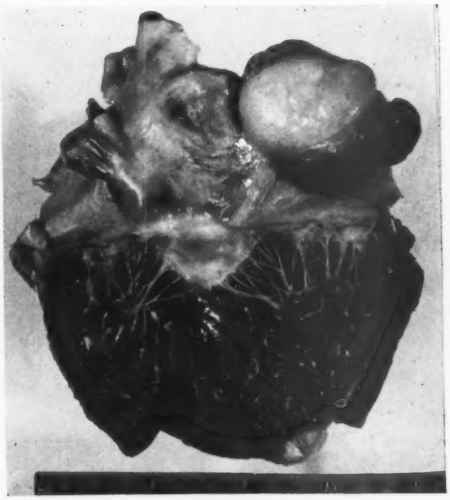

FIG. 2. Gross specimen of the myxoma of the left atrium. The tumor is retracted superiorly to show the pedicle.

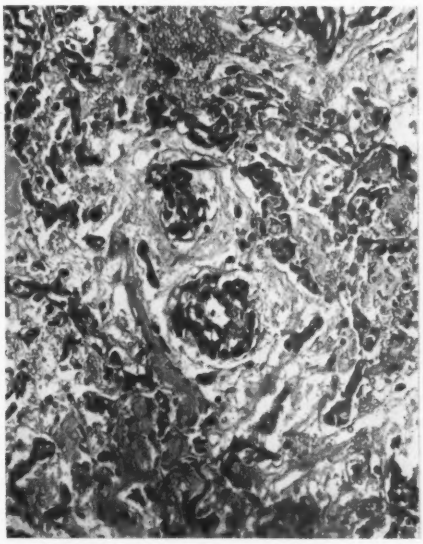

FIG. 3. Histologic section of the myxoma. The small vessels are prominent. (Masson trichrome stain; × 200.)

thickening of the walls of these vessels by small spindle cells imparted a peritheliomatous pattern. The intervening tissue was loose, myxomatous, and relatively acellular. An occasional stellate reticular cell as well as a rare macrophage was seen. Reticulum stains demonstrated fine and broad fibers coursing through the tumor but only occasionally were they

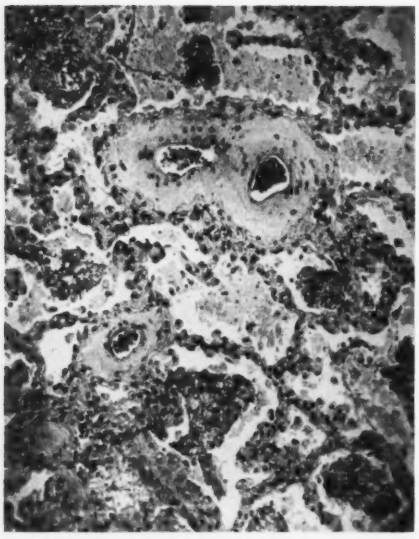

FIG. 4. Histologic section of the lung showing thickening and hyalinization of the walls of the pulmonary arterioles. (Hematoxylin and eosin, methylene blue; × 125.)

arranged around vessels. Invasion of the underlying atrial wall was not present.

The *right lung* weighed 575 Gm. and the left, 350 Gm. The pleural surface of the right lung was covered by a fibrinous exudate. The lower lobe contained several wedge-shaped, purple, firm areas ranging in size from 1.0 to 3.0 cm. In the lowermost portion there was a similar area, 5 cm. in diameter, with a softened center and, at its apex an adherent intra-arterial, soft, friable thrombus that histologically was partially organized. The *left lung* presented no pleural reaction but contained several additional small areas of infarction.

Microscopically, the walls of the pulmonary arterioles were greatly thickened and hyalinized (fig. 4).

The *liver* was finely nodular, brown and small, weighing 1070 Gm. The cut surface had a "nutmeg" appearance characteristic of acute hemorrhagic central necrosis.

The *adrenal glands* were bilaterally enlarged, weighing together 45 Gm. Grossly and histologically the cortices were thickened. The various zones were distinct, and abundant lipid was present.

The *anatomic diagnoses* were: Myxoma of the left atrium; cardiac hypertrophy; pulmonary infarction (multiple); thrombosis (embolus?) of small pulmonary artery; extensive hyalinization of pulmonary arterioles; acute hemorrhagic central necrosis of the liver; hyperplasia of the adrenal glands ("stress phenomenon").

DR. ERNSTENE: Were the changes in the pulmonary arterioles similar to those commonly present in patients who have mitral stenosis?

DR. MCCORMACK: The changes differed somewhat in that hyalinization was a much more prominent feature than is usual in association with mitral stenosis.

DR. HARRISON: Systemic arterial embolism has been reported in several instances of myxoma of the left atrium, the emboli consisting of fragments of neoplastic tissue or thrombotic material from the surface of the tumor. Was there any evidence of such emboli in this case?

DR. MCCORMACK: No. The endothelium was intact over the tumor, and there were no areas of ulceration or attached thrombi.

DR. ERNSTENE: This, then is a case of myxoma of the left atrium in which a number of features originally suggested the presence of mitral stenosis. Should a correct antemortem diagnosis have been made? The highly questionable presence of a mitral diastolic murmur and the absence of appreciable enlargement of the left atrium undoubtedly should have suggested, during the first period of observation, some process other than long-standing disease of the mitral valve. It appears also that insufficient attention was paid to the inconsistency between the elevation of pulmonary artery and pulmonary "capillary" pressures, on the one hand, and the lack of positive evidence of mitral stenosis, left atrial enlargement, or primary pulmonary disease on the other. This suggests that the obstruction to blood flow may have occurred at the orifices of the pulmonary veins rather than at the mitral valve. Will Dr. McCormack tell us whether this was possible from his necropsy findings?

DR. MCCORMACK: Our findings do not appear to make an obstruction of that kind very likely. When the heart was reconstructed, the tumor mass prolapsed into the orifice of the mitral valve.

DR. ERNSTENE: The paroxysms of dyspnea and orthopnea probably were due to temporary prolapse of that kind. But if chronic obstruction of the mitral valve orifice was the sole cause of the pulmonary hypertension that must have

been present for a considerable time to produce the changes in the pulmonary arterioles, it is strange that more than minimal dilatation of the left atrium should not have resulted. Chronic obstruction of the orifices of the pulmonary veins would explain the findings very well.

The abdominal pain that accompanied the attacks of paroxysmal dyspnea probably was due to a rapid increase in venous congestion of the liver, although physical examination did not give demonstrable proof of such a change.

To summarize, if one considers all aspects of the case and especially the doubt as to the presence of a diastolic apical murmur, the absence of definite enlargement of the left atrium, and the recurrent, abrupt changes in the circulation, a diagnosis of atrial tumor would have been warranted.

DR. HARRISON: It is of interest that at one time the decision to operate for the purpose of performing a mitral commissurotomy had been made, but circumstances forced a delay. Although the removal of tumors of this type appears feasible, it is doubtful that the lesion in the present case could have been extirpated through the customary approach by way of the left atrial appendage. An accurate diagnosis and the planning of an operation involving some such procedure as the "well" of Gross and his co-workers[2] might have led to a favorable outcome.

SUMMARY

A case of myxoma of the left atrium originally diagnosed as mitral stenosis has been presented. Analysis of the clinical and roentgenologic features and the data obtained from cardiac catheterization indicate that a correct diagnosis probably could have been made. Certain of the findings suggest that although prolapse of the tumor into the orifice of the mitral valve was responsible for striking changes in the patient's condition, the site of the chronic obstruction responsible for the pulmonary hypertension and the changes in the pulmonary arterioles may have been at the atrial orifices of the pulmonary veins.

REFERENCES

[1] PRITCHARD, R.: Tumors of the heart: Review of the subject and report of 150 cases. Arch. Path. **51:** 98, 1951.

[2] GROSS, R. E., POMERANZ, A. A., WATKINS, E., JR., AND GOLDSMITH, E. I.: Surgical closure of defects of the interauricular septum by use of an atrial well. New England J. Med. **247:** 455, 1952.

ABSTRACTS

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BACTERIAL ENDOCARDITIS

Laham, J., and Le Bozec, J. M.: Pathologic Q Waves in Osler's Subacute Infectious Endocarditis. Cardiologia **24:** 1 (Fasc. 1), 1954.

The authors present short case histories of five cases of subacute bacterial endocarditis with a similar electrocardiographic pattern; this is characterized by prominent Q waves in leads II and aV_F and particularly in lead III. One case came to autopsy and no confluent infarction was found grossly nor histologically.

The several possibilities which can account for this rather uniform pattern are pointed out. Posterior wall infarction due to coronary embolization, acute cor pulmonale, left ventricular hypertrophy in electrically vertical hearts and intraventricular conduction defects must be taken into consideration.

PICK

CONGENITAL ANOMALIES

Bayer, O., Rippert, R., Walter, H. H., and Loogen, F.: Clinical and Physiologic Findings in Ebstein's Syndrome. Ztschr. Kreislaufforsch. **43:** 98 (Feb.), 1954.

Clinical and cardiodynamic data are reported of three cases diagnosed during life as Ebstein's disease. The anatomic anomaly in this congenital malformation consists of a downward displacement of the tricuspid valve, with or without deformation of its posterior leaflet. This causes a subdivision of the right ventricular cavity in a distal and proximal portion, the former communicating with the right atrium. As in most of the reported cases, an atrial septal defect could be demonstrated in all three instances. The clinical picture is sufficiently characteristic to permit the diagnosis on the basis of physical, electrocardiographic and roentgenologic findings. The pertinent features consist of cyanosis with clubbing, reduplication of both heart sounds, systolic and diastolic murmurs, pronounced right bundle-branch block, a globular contour of the enlarged heart, and signs of right ventricular failure. The diagnosis can be fortified by cardiac catheterization, and typical dynamic, gasometric and spirometric findings are described. Of importance is the occurrence of sudden death. The condition must be differentiated particularly from Fallot's tetralogy because a shunt operation may have adverse effects and is, therefore, contraindicated in Ebstein's disease.

PICK

Bing, R. J., Reber, W., Sparks, J. E., Balboni, F. A., Vitale, A. G., and Hanlon, M.: Congenital Pulmonary Stenosis. J. A. M. A. **154:** 127 (Jan. 9), 1954.

The anatomic and physiologic findings in congenital pulmonary stenosis are described, and their implications for surgical treatment are discussed. Infundibular stenosis and narrowing of the subpulmonary tract are caused by muscular and fibrous obstruction. By making paraffin casts of the cardiac chambers, these findings of Brock are confirmed. In valvular pulmonic stenosis, there was no narrowing of the subpulmonary tract despite the existence of muscular hypertrophy. In pulmonary stenosis without associated septal defect, no intracardiac shunts were present. In pulmonary stenosis with auricular defect, or in the tetralogy of Fallot, the shunt was predominantly from right to left as pressures in the right ventricle were elevated. Valvulotomy in patients with valvular pulmonic stenosis was followed by a fall of pressure in the right ventricle and increased pulmonary blood flow. Construction of an artificial ductus in patients with

tetralogy of Fallot resulted in a decrease in oxygen content of the blood of the right auricle. Evidence of increased left-to-right intracardiac shunt was obtained from increased oxygen content of the blood from the right ventricle, and from elevated pressures in this ventricle.

KITCHELL

Burwell, C. S.: Patent Ductus Arteriosus and Vascular Rings. J. A. M. A. **154:** 136 (Jan. 9), 1954.

A patent ductus arteriosus is a functioning vascular connection between the aorta and the pulmonary artery. It has been shown that as much as several liters of oxygenated blood leak from the peripheral to the pulmonary circulation, forcing a larger than normal flow through the pulmonary arteries, capillaries, veins, the left auricle, and the left ventricle. Vascular rings are such abnormalities as double aortic arch, anomalous origin of the right subclavian artery, and right aortic arch. These exhibit an almost infinite variation and occasionally require no treatment. In some patients they produce symptoms and disability usually by compression of trachea, esophagus or bronchus, and in these, treatment may be vital. In the case of patent ductus arteriosus, operation should be thought of as essentially curative and should be used widely to prevent a development of complications. In the case of vascular rings, operation should be reserved for those who have a remediable anomaly producing disabling or threatening symptoms.

KITCHELL

Selzer, A.: Defects of the Cardiac Septums. J. A. M. A. **154:** 129 (Jan. 9), 1954.

Defects of the cardiac septums appear clinically as a number of well-defined syndromes that can be identified on clinical grounds or with the aid of cardiac catheterization. They range from a trivial shunt not materially affecting the circulation, to a most serious and disabling cardiac lesion. Atrial septal defect affects the circulation primarily by a large left-to-right shunt leading to a striking increase of pulmonary blood flow, dilatation of the pulmonary blood vessels, and hypertrophy and strain of the right heart. A late complication of this condition may be pulmonary hypertension. Occasionally, the flow through the defect reverses the usual direction leading to anoxemia and chronic cyanosis. Ventricular septal defects are of two types: small defects in which pressure differential between the two ventricles is maintained, and larger ones in which the pressure in two ventricles is identical. Smaller defects may show no important cardiac manifestations other than the characteristic murmur. However, a large left-to-right shunt increases the pulmonary blood flow to such proportions that changes in the pulmonary circulation are similar to those with atrial septal defect. With the large ventricular defect, the dynamic situation of a double outlet left ventricle is present, and in these cases severe pulmonary hypertension exists in the patient from the time of childhood, since the pulmonary arteriolar resistance is necessary for the maintenance of an adequate blood flow. Here pulmonary hypertension is the dominant clinical picture, and its degree determines whether the flow is primarily from left to right or from right to left. It is concluded that cases primarily best suited to surgical attempts to repair the septum are those in which a left-to-right shunt, large pulmonary flow, and little changes in intracardiac pressures are found.

KITCHELL

Bayer, O., Rippert, R., Walter, H. H., and Loogen, F.: Clinical and Physiologic Findings in Five Cases of Lutembacher Syndrome. Arch. Kreislaufforsch. **20:** 1 (Dec.), 1953.

Clinical, roentgenologic, electrocardiographic and catheterization data are presented of five cases considered to have Lutembacher's syndrome. In addition to an interatrial communication three had signs of mitral stenosis, one mitral stenosis and a patent ductus arteriosus, and one mitral insufficiency. The latter combination is termed by the authors "false Lutembacher." The etiology of these various combinations is probably not uniform and may be purely congenital or a combination of a congenital and an acquired (rheumatic) lesion.

The clinical picture of Lutembacher's disease is not characteristic. The most important criterion is found at roentgen examination and consists in a marked dilatation of the main pulmonary arterial trunk and of the left auricular segment which has an unusually high location on the left cardiac border. Catheterization in the presented cases revealed, apart from proving the interatrial communication, a pressure elevation in both atria and in the pulmonary capillaries. The pressure elevation in the right atrium is interpreted by the authors as being caused by pressure transmission from the left. With regard to clinical and hemodynamic findings, Lutembacher's syndrome stands between pure mitral stenosis and uncomplicated atrial septal defect. The combination of the two lesions can account for the absence of pulmonary congestion and the relatively long life expectancy of the patient. The occasional occurrence of cyanosis is explained by development of secondary pulmonary vascular changes causing pressure elevation in the right heart and a reversal of the shunt in the atria.

PICK

Swan, H. J. C., Zapata-Diaz, J., Burchell, H. B., and Wood, E. H.: Pulmonary Hypertension in Congenital Heart Disease. Am. J. Med. **16:** 12 (Jan.), 1954.

Cardiac catheterization studies disclosed no

significant difference in the pulmonary blood flow of patients with atrial septal defects, patent ductus arteriosus or ventricular septal defects, but did indicate that pulmonary arterial hypertension frequently occurred in patients with patent ductus arteriosus or ventricular septal defects and less commonly in patients with atrial septal defects. A mean pulmonary arterial pressure greater than 40 mm. Hg was observed in only 1 of 24 cases of atrial septal defect, but occurred in 10 of 24 cases with patent ductus arteriosus and in 14 of 20 cases with ventricular septal defects. Moderate or severe pulmonary hypertension, when present, was due to increased pulmonary resistance, since the pulmonary blood flow was usually decreased or within normal range. A high pulmonary resistance is essential for survival in many cases of ventricular septal defect and patent ductus arteriosus and may be due to a persistence of the fetal structure in the small pulmonary arteries and arterioles. Although an increased pulmonary flow may lead to the development of compensatory vascular changes to reduce excessive pulmonary flow as well as the development of degenerative vascular changes, the volume of flow alone cannot account for the development of the changes found in the pulmonary resistance, since the level of pulmonary blood flow was not significantly different among the three groups studied. It is suggested that factors of kinetic energy involved in the ejection of large volumes of blood from a high to a low pressure system, such as occurs in many cases of ventricular septal defect and patent ductus arteriosus, contribute important components to the pulmonary pressure pulse in these conditions that are absent in the pulmonary pulse associated with the usual cases of atrial septal defects.

HARRIS

De Carvalho Azevedo, A., Roubach, R., Ney Toledo, A., and De Carvalho, A.: Diagnosis and Surgical Treatment of Congenital Aortic Septal Defects. Acta Cardiol. **9:** 1 (Fasc. 1) 1954.

An operated case of aorticopulmonic fistula, partially repaired by suturing the defect, is presented and the main diagnostic criteria of this lesion are discussed on the basis of a review of the literature. Dyspnea on exertion is the most consistent symptom. The physical signs resemble those of a patent ductus, but the murmur is atypical in localization (usually at the left of the lower sternum) and, although systolic-diastolic, it is not continuous. X-ray is one of the most important aids for a correct diagnosis, showing bulging and dynamic pulsations of the ascending aorta, whereas, in a patent ductus, these signs involve mainly the aortic arch. The electrocardiogram is noncontributory. Cardiac catheterization is important because in the majority of reported cases there was pulmonary hypertension, and the exact location of the communication can be demonstrated by entering the aorta from the pulmonary artery. In contrast to a patent ductus, arterial oxygen determinations will give equal values in all four extremities. Venous angiography is not of great help apart from occasional demonstration of a venoarterial shunt, but retrograde aortography may clinch the diagnosis by visualization and precise outline of the area of the communication between the aorta and pulmonary artery.

PICK

CONGESTIVE HEART FAILURE

Weiss, R., and Steigmann, F.: Gitalin in the Treatment of Congestive Heart Failure. Am. J. M. Sc. **227:** 188 (Feb.), 1954.

Gitalin is described as a water soluble amorphous mixture of glycosides isolated from *Digitalis purpurea*. In the present study with this substance, digitalization and maintenance therapy was conducted in 49 cases of congestive heart failure. The total dose for digitalization ranged from 4.0 to 9.5 mg., averaging 5.9 mg. The daily maintenance requirements were approximately 0.5 mg. of the drug. In an effort to establish the ratio between the therapeutic and toxic dose levels the drug was administered in four patients until toxicity appeared; this ratio was about 42 per cent. In nine patients, doubling of the minimal therapeutic dose produced toxicity in two instances; five of these patients showed no toxicity at doses three to six times the minimal therapeutic level. The authors conclude that Gitalin is effective for the treatment of congestive heart failure and has a wide margin of clinical safety.

SHUMAN

Sonnek, P. J.: Congestive Heart Failure in the Elderly. Geriatrics **9:** 75 (Feb.), 1954.

To determine the importance of precipitating factors in congestive failure of the elderly, a survey was made of 50 cases who died and 50 who recovered and were discharged. The underlying causes in the first 50 patients who died were: arteriosclerosis, 64 per cent; arteriosclerosis with hypertension, 28 per cent; rheumatic heart disease, 4 per cent; tuberculosis, 2 per cent; and kyphoscoliosis, 2 per cent. Among the 50 discharged patients, arteriosclerosis occurred in 52 per cent, arteriosclerosis and hypertension in 44 per cent, rheumatic disease in 2 per cent, and syphilis in 2 per cent. The proportion of precipitating causes in the two groups are as follows, naming deaths first, discharges second: infections 18 per cent, 48 per cent; anemia 2 per cent, 6 per cent; pulmonary embolism 4 per cent, 4 per cent; physical and emotional strain 2 per cent, 12 per cent; economic factors 0, 2 per cent; insulin shock, 0, 2 per cent; injury 0, 2 per cent; cerebral thrombosis 8 per cent, 4 per cent; renal diseases 2 per cent, 0; tuberculosis 2 per cent, 0; Paget's disease 2 per

cent, 0; and unspecified factors 2 per cent, 4 per cent.

From the practical point of view, the best outlook for treatment was in those patients in whom the congestive heart failure was precipitated by extrinsic factors which could be treated.

RINZLER

CORONARY ARTERY DISEASE

Chandler, H. L. and Mann, G. V.: Heparin Treatment of Patients with Angina Pectoris. Failure to Influence Either the Clinical Course or the Serum Lipids. New England J. Med. **249:** 1045 (Dec. 24), 1953.

Thirteen patients (12 male and one female) with angina pectoris of two months' to six years' duration who received a total of 14 courses of heparin therapy form the basis of this report. The severity of angina pectoris was determined during a one- to four-week observation period prior to institution of any therapy. After this preliminary period, 10 cc. of a placebo solution of 5 per cent glucose in water was administered twice weekly intravenously. At varying intervals thereafter, 100 mg. of heparin dissolved in 10 cc. of water was substituted for the placebo. The time of such substitution was unknown to the subject and to the clinician. In the latter part of the study, injections were administered only once weekly. Placebo therapy was administered for 10 to 91 days in various subjects for a total of 867 subject days, and heparin treatment was given over periods of 28 to 151 days for a total of 1329 subject days (mean of 95 days per subject). The response to therapy was evaluated by the "report card" method; the weekly nitroglycerin intake, the percentage of "better" and "worse" days in regard to chest pain, repeated two-step tests, and the clinician's judgment based on an analysis of the information available.

Eleven subjects described improvement in their symptoms during the study. In nine, the improvement started during the period of placebo therapy and in only two did improvement first appear during the period of heparin therapy. The subject's feeling of improvement was generally supported by evidences of decreased nitroglycerin intake, but often the two did not coincide. With the exception of a diminished frequency of "worse" days in the heparin treatment period there was no difference of statistical significance in the analysis of "better" and "worse" days during placebo or heparin therapy. Twenty-six "two-step" tests were performed on nine patients at intervals during the study. There were no demonstrable effects of treatment upon the electrocardiographic responses. The total clinical evaluation showed that eight subjects experienced definite improvement during the investigative period, but this improvement was found not to have been influenced by the change from placebo to heparin or vice-versa. Serum lipoprotein and cholesterol determinations performed during the periods of heparin therapy showed no persistent effect for the interval of three or four days between injections nor any cumulative effect from prolonged treatment. No hemorrhagic disturbances or other untoward effects appeared during the period of heparin therapy.

The authors conclude that twice-weekly intravenous administration of 10 mg. of heparin in patients with angina pectoris resulted in no greater improvement than the injection of 5 per cent glucose in water in the same patients. In addition, heparin therapy had no persistent or cumulative effect on either the serum cholesterol or the serum S_f 12–20 or S_f 20–100 classes of lipoprotein.

SAGALL

Blumgart, H. L.: Treatment of Acute Myocardial Infarction with Particular Reference to Shock. J. A. M. A. **154:** 107 (Jan. 9), 1954.

Treatment in myocardial infarction aims to provide optimum rest to the patient's heart for healing of the infarct, and to prevent further damage from undue strain until a firm scar has been established and collateral circulation has developed. The importance of rest, the control of pain, the use of oxygen, aminophylline, digitalis, quinidine sulfate, procaine amide hydrochloride, glyceryl trinitrate (nitroglycerin), and anticoagulant therapy are discussed. It is pointed out that moderate to severe shock with systolic blood pressure below 80 mm. Hg may become irreversible or refractory to all methods of treatment within an hour. The need for early and energetic treatment with vasopressor drugs, plasma, or whole blood is thus indicated. The author discusses in detail the use of various vasopressor agents, particularly Arterenol. Proper treatment of shock has been demonstrated clinically to reduce the mortality of acute myocardial infarction to a significant though limited extent.

KITCHELL

Voigt, K. D. and Schrader, E. A.: Paper Electrophoretic and Arteriographic Investigations in Arteriosclerosis and Endangitic Arterial Occlusions. Ztschr. Kreislaufforsch. **43:** 2 (Jan.), 1954.

In 21 patients with obliterative disease of peripheral arteries proven by arteriography, serum proteins and lipids were determined by paper electrophoresis along with determinations of total and free cholesterol. Five cases with established arteriosclerosis showed an elevation of the α_2 globulins, of the β lipoprotein fraction and of free cholesterol. Two cases with definite endangiitis, on the other hand, showed no deviation from normal in the examined serum fractions. The authors believe that in cases in which the etiology of occlusive arterial disease cannot be established on clinical grounds—as in the 14 remaining cases of their material—study of the various serum fractions is of

value in classifying the patients either into the arteriosclerotic or endangiitic group.

PICK

Weiss, M. M., and Gray, W. R.: Hypertension and Myocardial Infarction in the Negro. Am. J. M. Sc. **227:** 186 (Feb.), 1954.

The authors studied the association between myocardial infarction and hypertension among Negroes admitted to a large general hospital. It was found that 90 per cent of the Negroes with myocardial infarction had hypertension. Of the males, 87.5 per cent had such a factor. Thus, myocardial infarction is infrequent in the absence of hypertension among these individuals.

SHUMAN

Edwards, J. E.: Pathology of Anomalies of Thoracic Aorta. Am. J. Clin. Path. **23:** 1240 (Dec.), 1953.

The author reviews in detail the pathology of the following entities: (1) patent ductus arteriosus; (2) aorticopulmonary septal defect; (3) aneurysm of an aortic sinus; (4) coarctation; (5) tubular hypoplasia of aortic arch, interruption of aortic arch; (6) "vascular rings"; and (7) Marfan's syndrome.

MCKUSICK

ELECTROCARDIOGRAPHY

Rieger, P.: On Some Physical Problems of the Electrocardiogram. Cardiologia **24:** 47 (Fasc. 1), 1954.

On the basis of experiments performed on excised frog hearts, the author discusses the causes of differences in the amplitudes of electrocardiographic leads, in the location of the point zero, and in the integrated vector, when the leads were arranged in one plane or spatially. Whereas, with spatial recordings, the electrical center coincides with the center of the part of the heart under activation (the atria or the ventricles), with leads recorded in a single plane it approaches the center of the entire heart. Furthermore, in a plane the magnitude of recorded potentials decreases in proportion to the distance of the lead while in the space it does so proportionally to the square of the distance.

The human body is an electrically nonhomogeneous medium with varying electric resistances in different tissues. Precordial leads reflect potentials transmitted mainly over the mediastinum and the diaphragm, which correspond to a plane rather than to a volume conductor. In practice the conditions in chest leads are likely to be intermediate between the two extremes. These considerations may account for certain variations of abnormal deflections, depending on the site and the extent of the lesions present.

PICK

Schaub, F., and Wegmann, T.: Electrocardiographic Alterations in Funnel Chest. Cardiologia **24:** 39 (Fasc. 1), 1954.

The authors report electrocardiographic observations in 108 patients with a depressed sternum, ranging in age from 16 to 50 years, none of whom had clinical evidence of cardiac or pulmonary disease. In the majority of cases there was right axis deviation. In 12 per cent disturbances of rhythm (premature beats and ectopic rhythms) were recorded. In 59 per cent of the P waves and 51 per cent of the QRS complexes, there were anomalies consisting of notching and slight widening. In six cases the electrocardiographic pattern suggested the presence of incomplete right bundle-branch block. The S-T segments were normal in all, but the T wave was frequently inverted in the right sided chest leads, including V_3 or V_4.

In most of the cases all alterations can be accounted for by an abnormal position and/or rotation of the heart caused by the thorax deformity. The significance of these changes, which are to a certain extent characteristic but not specific for a funnel chest, lies in the fact that they may be misinterpreted unless the chest deformity is taken into consideration.

PICK

Segers, M., Van Dooren, F., Boyadjian, N., Uyttenhove, P., Van Houte, O., and Delatte, E.: Differentiation of True and False Patterns of WPW. Acta Cardiol. **9:** 59 (Fasc. 1), 1954.

Examples are presented and discussed of doubtful pre-excitation patterns requiring long records or additional studies in order to establish the correct diagnosis. This refers to the following instances: cases in which an abnormal P wave with prolonged duration encroaches upon QRS, thus seemingly shortening the P-R interval; cases with abnormal ectopic impulse origin in the atria in the presence of intraventricular block; cases in which the anomalous QRS component (delta wave) is obvious only in certain leads, e.g., over the left precordium, or is simulated by a slurred and widened Q wave due to posterior wall infarction; and finally, escapes or late diastolic ventricular premature systoles, inscribed just after a sinus P wave may simulate ventricular preexcitation. The differential diagnostic criteria applying to such instances are indicated.

PICK

Nickerson, J. L., and Mathers, J. A. L.: A Study of the Physical Properties of the Ballistocardiograph. Am. Heart J. **47:** 1 (Jan.), 1954.

Displacement ballistocardiographs of each of seven subjects with an age range of 18 to 79 years were recorded in the resting state with four different ballistic systems. These systems were, respectively, (1) the low frequency, critically damped system; (2) a middle frequency, partly damped system; (3)

a high frequency, partly damped system; and (4) a direct ballistocardiograph where the body alone is the oscillating system. One subject had coarctation of the aorta; the other six were healthy. Fournier analyses of the displacement ballistocardiograms were made for the four types of instruments. The coefficients of these series were corrected for the distortion introduced by the ballistic bed and by transmission through the body. In comparing the coefficients of these basic series with those of the original series obtained from the analyses of patterns of the various instruments, the best agreement was obtained from the low frequency, critically damped ballistocardiograph.

RINZLER

Kelly, J. J. Jr., Caccese, A., Ortiz-Marquez, J., and Taubman, F.: The Effects of Cigarette Smoking on the Ballistocardiograms of High School Youth. Am. Heart J. **47:** 30, (Jan.), 1954.

Ballistocardiograms were taken on 100 high school boys between the ages of 14 and 18 years with a Dock type of electromagnetic ballistocardiograph. All were healthy and habitual smokers for 2 to 5 years. The records were obtained during normal respiration. A control tracing was taken and then a second tracing was obtained after the final puff of a standard cigarette. No real abnormalities in the ballistocardiogram occurred. A significant increase in respiratory variation of the I-J waves (Grade 1) occurred in only two subjects; lesser increase in this variation was noted in three others. The most frequent response to smoking was an increase in pulse rate, with minimal evidence of change in stroke volume, judging from the amplitude of the systolic waves.

RINZLER

Zapfe, H., and Nehls, M.: The Electrocardiographic Diagnosis of a Scar on the Posterior Wall. Ztschr. Kreislaufforsch. **42:** 908 (Dec.), 1953.

The author studied the usefulness of various types of electrocardiographic leads in the diagnosis of healed myocardial infarction on the posterior wall. Recorded were the three standard leads, unipolar leads by Goldberger's technic, chest leads according to the method of Nehb, a dorsal chest lead and esophageal leads. Most information was obtained from esophageal leads; the six limb leads were second. Difficulties which may arise in the evaluation of a Q wave in the esophageal leads are pointed out.

PICK

Fowler, N. O., and Helm, R. A.: The Spatial Angle (θ) between the long Axis of the QRS loop and the Longitudinal Axis of the Ventricles. Am. Heart J. **46:** 821 (Dec.), 1953.

Twenty-five patients were used in this study. An estimation of the spatial angle (θ) between H and the long axis of the QRS loop was made. H was determined from chest teleroentgenograms. The position of the QRS loop was studied by three methods: (1) by a modification of the method of Grant (VECG); (2) from plane projections of the spatial QRS loop recorded from a cube reference frame; (3) from projections of the spatial QRS loop recorded from an equilateral tetrahedron reference frame. The mean values of θ were 50 degrees (cube); 46.6 degrees (tetrahedron); 59.2 degrees (VECG). Although the mean values of θ and its frontal and sagittal projections were not significantly different when determined by the three systems, significant association between the position of H and the QRS loop suggests difficulty in predicting the anatomic heart position from the long axis of the QRS loop. No conclusion could be reached with regard to the relative accuracy of the three methods of estimating the QRS loop position, or with regard to the relative accuracy of frontal and sagittal plane projections of the long axis of the QRS loop. No evidence was found to indicate that the VECG method of estimating QRS loop position is less accurate than the other two methods employed. This applies only to the axis of the loop and does not imply that routine nonsimultaneous precordial leads may be used to derive a spatial QRS loop.

RINZLER

Starno, A., Filocamo, G., and Testoni, G.: The Duration of Isometric Contraction of the Right Ventricle. Cardiologia **24:** 65 (Fasc. 2), 1954.

In 15 patients with various types of cardiovascular disease, the time of isometric contraction of the right ventricle was determined from intracavitary pressure curves (recorded by the method of Condorelli) and simultaneous electrocardiograms. The values were obtained by determination of the time relationship between the beginning of the QRS and the onset of the systolic wave of the ventricular pressure curve, or by measuring the time interval between onset and peak of the systolic wave in the atrial pressure curve.

In subjects with normal hearts and in cardiac patients with normal pulmonary arterial pressures, the average duration of the phase of isometric contraction was found to be 0.031 second and 0.033 second, respectively. In patients with pulmonary hypertension it attains 0.04 second. However, no constant relationship exists between the duration of isometric contraction and the degree of pressure elevation in the pulmonary circulation.

PICK

Lepeschkin, E.: Interrelations between Hiccup and the Electrocardiogram. Am. J. Med. **16:** 73 (Jan.), 1954.

In five cases of recurrent hiccups, the hiccup sounds were recorded synchronously with three

leads of the electrocardiogram. In three cases, the hiccup movements caused electrocardiographic artefacts which could be confused with U waves or with auricular and ventricular premature contractions. The hiccup sounds, as well as the artefacts, always occurred 0.17 to 0.40 seconds after the beginning of the QRS complex of the electrocardiogram, and, in some cases, two successive heart beats were followed by hiccup movements. It is postulated that, in the reported cases, the hiccup was caused by stimulation of one of the phrenic nerves by the electric currents registering as the QRS complex of the electrocardiogram. The hyperirritability of the phrenic nerves in the reported cases was probably due to a decrease in the ionized serum calcium or to alkalosis.

HARRIS

Starr, I., and Schnabel, T. G., Jr.: Studies Made by Simulating Systole at Necropsy. III. On the Genesis of the Systolic Waves of the Ballistocardiogram. J. Clin. Investigation. **33:** 10 (Jan.), 1954.

The authors describe the technic and results obtained by simulating systole in a cadaver lying on a ballistocardiograph. After a systemic diastolic pressure had been secured by an infusion of blood into the femoral artery, simultaneous injections of blood into the aorta and pulmonary artery produced a cardiac systole. Experiments were performed under different conditions of stroke volume and blood pressure in both normal and arteriosclerotic subjects.

Under the conditions of this study, it appears that the amplitude of the resulting ballistocardiogram, determined by the vertical distance between the I and J wave tips, correlates well with cardiac outputs under certain conditions. A better correlation was found between the square root of the amplitude of the ballistocardiogram $(\sqrt{I + J})$ and the maximum velocity of ejection. When the body surface area was included in the equation, the correlation was very high (0.92).

The point of particular interest is the observation that a correction for body size improves the estimate of the heart's force from measurements made on the ballistocardiogram. The authors conclude that it is entirely reasonable to employ the ballistocardiogram to estimate cardiac force in relative terms.

WAIFE

Talbot, S. A., Deuchar, D. C., Davis, F. W., Jr., and Scarborough, W. R.: The Aperiodic Ballistocardiograph. Bull. Johns Hopkins Hosp. **94:** 27 (Jan.), 1954.

Current ballistocardiographic systems employ a heavy, rigid table on which the body evokes spring and damping forces from the soft tissues of the dorsum of the subject. These forces contribute to the finished ballistocardiogram oscillations which have no cardiovascular significance. The authors have recorded the acceleration ballistocardiogram in the head-foot axis in subjects on a very light platform floated on mercury. The resulting "aperiodic ballistocardiogram" in normals reveals a consistent pattern which is compared by the authors with Starr-type records. It is their impression that aperiodic recording will permit a closer correlation of ballistocardiographic form with physiologic factors.

MCKUSICK

Smith, J. E., and Rosenbaum, R.: Studies of the Effect of a Second Degree of Freedom in Ballistocardiography. Am. Heart J. **46:** 799 (Dec.), 1953.

In this report, the engineering usage of the two degrees of freedom is used and refers to two masses connected by a spring or springs. All motions refer to the head-foot direction and the degrees of freedom are (a) motion of the body in reference to a fixed point in space, and (b) the motion of the platform in the Dock type leg-mounted ballistocardiograph with respect to a fixed point in space. For faithful recording of the motion of the body with a Dock type of pickup, the pickup frequency should be at least 14 times the frequency of the body. For recording of the cardiovascular forces, a pickup frequency of approximately six times the body frequency appears to yield clinically valid data (although clinically significant data were obtained with a frequency ratio of 4). Further study of the significant frequency components in the cardiovascular forces is needed before an optimum value of pickup frequency can be determined. An analysis of the frequency components of the forcing function (by Fournier analysis) for a large number of abnormal and normal subjects is needed. By means of an elastic stocking and a five-ounce pickup, it is possible to maintain a pickup frequency at approximately 35 cycles. By the simple addition of weight to the platform, the natural frequency of the pickup can be lowered and controlled as desired. It can readily be seen that distortion from different body frequencies can be kept small with a platform frequency of 35 cycles, since a body frequency of 4 would have a delta of approximately 9, and a body frequency of 6 would have a delta of approximately 6. Thus, over a fairly large portion of the frequency range, the relative distortion between these two values of delta (6 and 9) is negligible. The problem of the system of two degrees of freedom may be as important in the table type of ballistocardiograph as in the Dock type. In the ballistic table type of ballistocardiograph, the complete system must be treated as a two-degrees-of-freedom system, in which the first degree of freedom is the body mass with its characteristic damping and natural frequency, and the second degree of freedom is represented by the

table and natural frequency and damping. An improper choice of table, the characteristics of which are affected by the mass of the body placed on it, may result in distortion of the signal coming from the pickup to the extent that the data so obtained are meaningless.

RINZLER

ENDOCRINE EFFECTS ON CIRCULATION

Code, C. F., Mitchell, R. G., and Kennedy, J. C.: The Effect of Cortisone on the Number of Circulating Basophils and Eosinophils: Proc. Staff Meet. Mayo Clinic. **29:** 200 (April), 1954.

Administration of cortisone reduces the number of tissue basophils (mast cells) seen in sections of various tissues. The present study demonstrates that cortisone affects the number of basophils in the blood of human beings in a similar fashion. If these observations are substantiated, the possibility may be raised again of a relationship between the tissue or fixed mast cells and those that circulate. At least it seems that both are similarly affected by cortisone.

The results of this study allow the definite conclusion that cortisone reduces the number of basophils in the circulating blood of healthy human beings in a way very similar to that in which it reduces the number of eosinophils in the blood. The parallelism is sufficiently close to indicate a relationship between the basophils and the eosinophils of the blood of healthy persons. Whether this numerical relationship reflects a fundamental physiologic or functional association between the two types of cells is not established by the study.

SIMON

HYPERTENSION

Klek, J., and Fazekas, J. F.: The Use of Apresoline in the Hypertensive Arteriosclerotic Syndrome. Am. J. M. Sc. **227:** 57 (Jan.), 1954.

The use of hypotensive agents in elderly patients with arteriosclerosis and elevated blood pressures has been viewed with suspicion because of the dangers involved in reducing the blood flow to the kidneys, brain and coronary vessels. However, it has been found that Apresoline will increase renal flow and cardiac output and will decrease cerebral vascular resistance while producing a drop in hydrostatic pressure. In this study, 17 elderly hypertensive patients received Apresoline in gradually increasing doses beginning with 25 mg. four times daily. The drug was alternated with placebo therapy in a number of patients. No cerebral or cardiorenal complications were noted. Only one patient experienced distressing side effects. Studies of cerebral hemodynamics revealed a decrease in cerebral blood flow. Marked improvement in the signs of cerebral circulatory insufficiency was observed. However, the cerebral metabolic rate remained unchanged. A fall in blood pressure was noted in 16 of the patients with clinical improvement in 14 patients.

SHUMAN

Freis, E. D., Rose, J. C., Partenope, E. A., Higgins, T. F., Kelley, R. T., Schnaper, H. W., and Johnson, R. L.: The Hemodynamic Effects of Hypotensive Drugs in Man. III. Hexamethonium. J. Clin. Investigation **32:** 1285 (Dec.), 1953.

The effects of hexamethonium were studied in 25 hypertensive and 4 normotensive subjects. The drug was administered intravenously at a rate of 1 to 2 mg. per minute for the first 15 mg. and then at a rate of 5 mg. per minute until either a significant hypotensive effect was obtained, or until 50 to 100 mg. had been administered. Observations on the hemodynamic effects revealed that in the absence of cardiac decompensation, hypertensive patients have a decrease in cardiac output and right heart pressure. There was no significant change in peripheral resistance. These alterations may be the result of venous "pooling" or failure of reflex vasoconstriction.

When cardiac failure is present, the hypotensive effect is accompanied by an increase in cardiac output and a significant decrease in total peripheral resistance. These effects may be mediated by an unloading of the congested right side of the heart and inhibition of those vasoconstrictor reflexes which are activated by the low output failure.

Other observations suggest that the blood flow through the muscles is only moderately increased and the hepatic-portal blood flow decreased after hexamethonium.

Certain hemodynamic responses to hexamethonium may not be entirely desirable. For example, cardiac output may decrease, renal clearances (especially the glomerular filtration rate) may fall, at least temporarily, and vasomotor reflexes essential to homeostasis may be seriously compromised. Nevertheless, the results of hemodynamic analysis need not always indicate the desirability of a drug in clinical practice where other factors may determine its usefulness.

WAIFE

Rosenman, R. H., Freed, S. C., St. George, S., and Smith, M. K.: Effect of Varying Dietary Potassium upon the Blood Pressure of Hypertensive Rats. Am. J. Physiol. **175:** 386 (Dec.), 1953.

When dietary intake of potassium is severely restricted, the blood pressure in hypertensive rats is reduced markedly. This confirms earlier work. When restrictions were less marked, the hypotensive effect was also less.

OPPENHEIMER

Jeffers, W. A., Zintel, H. A., Haffkenschiel, J. H., Hills, A. G., Sellers, A. M., and Wolferth, C. C.: Evaluation of Adrenal Resection and Sympathectomy in Ninety-Nine Persons with Hypertension. J. A. M. A. **153:** 1502 (Dec. 26), 1953.

Ninety-nine patients with severe hypertension have been treated by sympathectomy of the Adson or Smithwick type with subtotal or total adrenalectomy. The Adson sympathectomy, combined with adrenal resection, is performed in two separate stages and has been well tolerated by most patients with adequate renal function. Their convalescence has been easier than that of those patients having thoracolumbar sympathectomy. It will require further observation to establish whether, or under what circumstances, this type of operation will prove superior in the long run to (1) thoracolumbar sympathectomy, (2) thoracolumbar sympathectomy plus subtotal or total adrenalectomy, or (3) total adrenalectomy alone. These operations cannot be attempted without a well-integrated medical and surgical team prepared to deal not only with all surgical complications but with any of the manifestations of severe hypertensive cardiovascular disease or with adrenal insufficiency. Each patient must have prolonged and careful follow-up with a member of the team on call at all times to treat acute adrenal insufficiency or any other emergency. The authors state that to date they have encountered no greater difficulty in managing patients after total adrenalectomy than after subtotal adrenalectomy. The most frequently encountered symptom is a mild intolerance of cold. To be eligible for operation patients had (a) an average diastolic blood pressure of 120 mm. Hg or more, (b) lack of response to intensive medical therapy, and (c) evidences of progressive vascular damage. Contraindications include any one with the following factors: (a) poor renal function, (b) less than 6 months' convalescence from a stroke or coronary occlusion, (c) age over 55 years, or (d) inability, for any reason, to cooperate in taking adrenal cortical replacement therapy. During the period of postoperative observation, 23 per cent of the 99 patients showed excellent response, 23 per cent fair response, and 30 per cent poor response; 24 per cent died. Only one patient died from uncomplicated adrenal insufficiency. The usual cause of death was a stroke or coronary occlusion. Patients with paroxysmal dyspnea or congestive heart failure prior to operation showed the most striking improvement. Most of those subjected to subtotal adrenalectomy required adrenal cortical replacement therapy after operation. Objective changes have been observed in improvement of the heart size, retinopathy, and electrocardiographic findings.

KITCHELL

Vetter, H., Grabner, G., Miczoch, F., and Steinbereithner, K.: Cardiac Catheterization in Pronounced Pressure Reduction Caused by Hexamethonium. Klin. wchnschr. **32:** 97 (Feb.), 1954.

The authors studied the alterations of the peripheral and pulmonary circulation in 16 patients treated with hexamethonium prior to surgery or for medical indications. Three cases had no evidence of cardiovascular disease, five cases were hypertensive, and the rest had symptoms and signs compatible with increased right ventricular load.

Hexamethonium chloride applied intravenously in doses sufficient to lower the mean systemic pressure to an average value of 60 mm. Hg causes, in addition, pressure reduction in the pulmonary vascular system and a decrease of venous filling pressure. This takes place with a reduction of total resistance in the peripheral and systemic circulation, while the calculated pulmonary arteriolar resistance remains unchanged. The work of either ventricle was found to be considerably decreased after the treatment and the arteriovenous oxygen difference increased by reduction of the venous oxygen saturation.

These findings are discussed with regard to their theoretic and practical significance and to certain questions relative to the therapy of systemic and pulmonary hypertension and heart failure.

PICK

Houck, C. R.: Effect of Hydration and Dehydration on Hypertension in the Chronic Bilaterally Nephrectomized Dog. Am. J. Physiol. **176:** 183 (Feb.), 1954.

After bilateral nephrectomy, dogs were maintained on a low salt diet by intermittent peritoneal dialysis. In the absence of dehydration there was hypertension if weight and extracellular fluid volume increased. When there was dehydration and no increase in extracellular fluid, hypertension did not develop. Dehydration of hypertensive animals caused some reduction in blood pressure but not to normal. Severe dehydration produced hypotensive shock while rehydration restored blood pressure to hypertensive levels. These experiments suggest a causal relationship between increased body fluids and hypertension. It is not necessary to maintain the increased body fluids to maintain the hypertension.

OPPENHEIMER

Rosenblatt, W. H., Haymond, T. A., Bellet, S., and Koelle, G. B.: The Effect of Single Intravenous and Oral Doses of McN-181(1,4 BIS(1,4-Benzodioxan-2-Ylmethyl) Piperazine) upon the Blood Pressure of Hypertensive Subjects. Am. J. M. Sc. **227:** 179 (Feb.), 1954.

The authors studied the effects of a product known as McN-181 in hypertensive subjects. This is described as a piperoxan found by laboratory

investigation to be a highly potent adrenergic blocking agent with a low order of toxicity. The patients employed were those with benign essential hypertension; the drug was administered both by oral and intravenous routes. On six occasions, a moderate reduction in systolic and diastolic pressure occurred after intravenous infusion of the agent, the hypotensive effect usually persisting 30 to 60 minutes after the infusion. In four instances, there was no significant pressure change and a pressor effect was noted twice in one patient. A slow infusion was more effective in lowering the blood pressure while rapid infusion resulted in an increase in heart rate, possibly due to a direct action of the drug on the myocardium. With oral therapy, varying degrees of reduction occurred in five of the six trials. Because the drug is capable of reducing blood pressure in certain hypertensive patients, it is worthy of consideration for long-term assessment for the treatment of hypertension.

SHUMAN

Fregly, M. J.: Effects of Extremes of Temperature on Hypertensive Rats. Am. J. Physiol. **176:** 275 (Feb.), 1954.

Exposure to cold (5 C.) for 20 days elevates blood pressure in normal rats while similar exposures in hypertensive rats produce no change. Temperatures of 35 C. increased pressure in controls but not in hypertensive rats. Similar food intakes at 5, 25 and 35 C. in both groups suggest that total body heat production is the same in control and hypertensives. Polydipsia and polyuria were present in renal hypertensive rats in air at 25 C. They chose more potassium solution to drink and less sodium than controls. Air at 5 C increased fluid intake and urine production in these rats. Although hypertensives and controls took in more sodium and potassium when exposed to cold, the hypertensives took in significantly less sodium. Air at 35 C. increased the intake of total fluid, water and potassium in controls but not in hypertensives. When exposed to heat, both groups had smaller sodium and potassium intakes. Hypertensives had a greater mortality at temperature extremes than controls.

OPPENHEIMER

Hafkenschiel, J. H., Crumpton, C. W., and Friedland, C. K.: Cerebral Oxygen Consumption in Essential Hypertension. Constancy with Age, Severity of the Disease, Sex, and Variations of Blood Constituents, as Observed in 101 Patients. J. Clin. Investigation. **33:** 63 (Jan.), 1954.

A group of 101 hypertensive patients were studied. All had a diastolic pressure persistently above 100 mm. Hg and evidence of retinopathy, electrocardiographic damage, or impaired renal function. Cerebral hemodynamics and metabolic studies were made by the nitrous oxide method.

The results indicate that despite a mean increase of 75 per cent in cerebral vascular resistance, the blood supply to the brain is automatically adjusted to its oxygen requirements, thus maintaining the cerebral blood flow within the normal rage. The oxygen consumption of the brain in hypertensives is not significantly different from that of normotensives, and does not vary appreciably in patients of different sexes, ages, or prognostic group.

The data obtained suggest that the cerebral oxygen consumption varies directly with the blood flow and inversely with the vascular resistance. It would seem that the oxygen consumption in hypertension is kept constant by a reciprocal relationship between the blood flow and the arteriovenous oxygen difference, keeping the jugular oxygen tension above 25 mm. Hg.

WAIFE

Arnold, O. H., and Bock, K. D.: Malignant Hypertension. Ztschr. Kreislaufforsch **43:** 16 (Jan.), 1954.

Based on the analysis of five of their own observations, the authors discuss criteria for the diagnosis of malignant hypertension. Most important is the finding of permanent elevation of the diastolic pressure over 120 mm. Hg, uninfluenced by bed rest and treatment, with manifestations of impaired blood supply to vital organs. The latter includes ischemic manifestations of the brain (e.g. cerebral accidents at a relatively young age, papilledema, retinitis and hemorrhagic foci), of the heart (clinical and electrocardiographic evidence of diffuse myocardial damage) and of the kidneys (proteinuria and hematuria, abnormal concentration and clearance tests). If only a few of these signs are present and not too pronounced, a certain period of observation is necessary in order to establish the progressive character of the disease. Simultaneous occurrence of several ischemic alterations in the presence of elevated diastolic pressure justifies an immediate diagnosis of malignant hypertension.

PICK

Hafkenschiel, J. H., Friedland, C. K., and Zintel, H. A.: The Blood Flow and Oxygen Consumption of the Brain in Patients with Essential Hypertension before and after Adrenalectomy. J. Clin. Investigation **33:** 57 (Jan.), 1954.

The authors report their observations on the effect of subtotal adrenalectomy (approximately 90 per cent) on arterial and jugular venous blood constituents and cerebral metabolism in patients with hypertension. Although the cerebral blood flow increased slightly after adrenalectomy, the mean values of oxygen consumption, the venous oxygen content, and venous oxygen tension remained essentially unchanged. It was found that the high cerebral vascular resistance in hypertension was lowered by adrenalectomy. The reduction in resistance, as well as the mean decrease in arterial

pressure, appeared to be greater after combined sympathectomy-adrenalectomy than after sympathectomy alone. These data suggest that the increased cerebral vascular tone in certain hypertensive patients is reversible.

WAIFE

Bowers, R. F.: Bilateral Adrenalectomy for Severe Hypertension. J. A. M. A. **154:** 394 (Jan. 30), 1954.

Experiences with bilateral partial adrenalectomy for severe hypertension in 27 patients are discussed. There were six postoperative deaths. Twenty of the 21 survivors now have normal blood pressures, and some of the patients have been followed for as long as 20, 21, and 22 months. Symptomatic improvement of hypertensive symptoms was obtained in all survivors, and hypoadrenalism was present in all of them. Experience with these 27 cases permits these suggestions: (1) Indications are known and can be fairly accurately estimated; (2) the preoperative and immediate postoperative care are easily and safely established; (3) operation is not difficult for the operator accustomed to gastric or pancreatic surgery; and (4) the only phase that denies the procedure the dignity of being routinely recommended is the maintenance management. The author, however, feels that with the present hormonal substitutive drugs and a reasonable hope for better agents in the future the dangers can be successfully overcome.

KITCHELL

Doniach, L., Morrison, B., and Steiner, R. E.: Lung-changes during Hexamethonium Therapy for Hypertension. Brit. Heart J. **16:** 101 (Jan.), 1954.

Of 54 severely hypertensive patients treated with parenteral hexamethonium bromide, three developed unexpected pulmonary dyspnea with radiologic evidence of pulmonary fibrosis. Two of the three patients died, and their lungs showed a mixed intraalveolar and interstitial fibrosis associated with preservation of the normal alveolar elastic pattern. These changes are not attributed to the drug but rather to attacks of left heart failure modified by intermittent lowering of the blood pressure by hexamethonium. The treatment prolonged life and thereby made possible the development of carnification.

SOLOFF

Tenney, B.: Hypertension in Pregnancy. New England J. Med. **249:** 1108 (Dec. 30), 1953.

Hypertensive disease in pregnancy may be classified into three groups: essential hypertension (patients with pre-existing vascular disease); renal disease (patients with pre-existing renal disease); and pre-eclamptic toxemia and eclampsia. Edema in itself is a common clinical finding in pregnancy and of no particular importance in relation to the development of hypertension. This retention of fluid results from sodium retention.

Renal disease in pregnancy is a very serious complication with a poor prognosis for mother and baby. Patients with chronic kidney damage may have sufficient renal reserve in the nonpregnant state to live in good health. The increased kidney load of pregnancy may precipitate the signs and symptoms of renal disease. With repeated pregnancies signs of renal damage tend to appear earlier and become more severe. Chronic renal disease is associated with less than 50 per cent prognosis for survival of the child. The treatment of chronic nephritis in pregnancy consists primarily of avoiding excessive weight gain and retention of fluid and electrolytes as well as sufficient rest. A high protein low-sodium diet is recommended. At the earliest sign of renal failure, the pregnancy should be terminated. In the last month of pregnancy renal failure and/or death in utero of the baby are most likely to occur, and termination of the pregnancy should be seriously considered at this time. The patient with very mild nephritis with no signs of toxemia and without increasing renal or vascular damage or hypertension may be allowed to go to term and deliver spontaneously.

With mild pre-existent hypertension the prognosis for the pregnancy is usually good and is better than for the patient with chronic renal disease. The author believes that essential hypertension is unaffected by pregnancy unless a superimposed pre-eclamptic toxemia develops. These patients should be watched carefully for any rise in blood pressure or the development of albuminuria. These findings warn of impending pre-eclampsia. This usually occurs in the third trimester. If pre-eclampsia develops, the pregnancy should be terminated. Treatment of essential hypertension in pregnancy is aimed at the prevention of pre-eclamptic toxemia mainly by preventing water and electrolyte retention. The patient should be on an extremely low sodium intake. With the development of any edema or excessive weight gain, the patient should be hospitalized and attempts made to induce a diuresis. The type of delivery depends on the individual case. If the patient passes through the pregnancy uneventfully, there is usually no harm done and further pregnancies are relatively safe, despite the presence of hypertension.

Pre-eclamptic toxemia is a hypertensive state which appears usually in the last trimester and disappears after the pregnancy has terminated. The condition is indicated by the appearance of an increase in blood pressure (especially diastolic) over pre-existing levels and albuminuria. In most cases these findings are preceded by a marked increase in weight from fluid retention. Visual and cerebral symptoms develop as the disease progresses. The treatment of pre-eclamptic toxemia has to be

individualized. With mild cases the aims of therapy consist of rest, low sodium diet, and diuresis to reduce fluid retention. A pre-eclamptic toxemia with a blood pressure of over 160 systolic and particularly over 100 diastolic must be considered a serious case. Excessive albuminuria, the presence of cerebral or visual symptoms, or a marked rapid weight gain also indicate a severe case. In such cases the early or immediate termination of pregnancy has to be considered. Hypotensive drugs and magnesium sulfate may be of some value in therapy.

Eclampsia is the terminal stage of pre-eclamptic toxemia and is manifested by convulsions, coma or both. Pregnancy in patients with severe pre-eclampsia should be terminated before eclampsia develops. With eclampsia, anuria and oliguria are common along with other signs of renal failure. The immediate treatment of eclampsia is the control of the convulsion and the coma. Once the patient has recovered from the convulsions delivery should be performed by rupturing the membranes or by cesarean section.

SAGALL

Kubicek, W. G., Kottke, F. J., Laker, D. J., and Visscher, M. B.: Adaptation in the Pressor-Receptor Reflex Mechanisms in Experimental Neurogenic Hypertension. Am. J. Physiol. **175:** 380 (Dec.), 1953.

Arterial blood pressure and pulse rate were studied during chronic splanchnic nerve stimulation. After 20 hours of continuous stimulation, the pulse rate was normal during the hypertension. A tachycardia appeared as the blood pressure declined. The pressor receptor and/or the central pathways may adapt to the hypertension without bradycardia or vasodilation. Permanent hypertension could not be produced even though the blood pressure was elevated 30 mm. Hg 20 hours a day for 28 consecutive days. At the end of stimulation, pressure returned to control values within a few minutes. During this prolonged stimulation of the nerve, it did not loose its ability to respond.

OPPENHEIMER

West, J. R.: Pulmonary Hypertension. Bul. N. Y. Academy Med. **30:** 67 (Jan.), 1954.

In a variety of disorders of the heart and lungs, an increase occurs in the normal low hydrostatic pressure within the pulmonary vascular bed. Incomplete systolic emptying of the left ventricle, which is not balanced by a similar immediate change in the right ventricular emptying, will result in a greater temporary right ventricular output, thus producing pulmonary congestion. The shift of blood from the systemic circulation to the pulmonary circulation increases the pulmonary blood pressure. Increased pulmonary pressure in mitral stenosis is not a compensatory response to maintain an adequate cardiac output in the face of valvular obstruction, but is a reflection of the state of equilibrium between the various factors regulating cardiac output and the impedance of blood flow due to the valvular obstruction. Severe pulmonary hypertension may result from changes in the pulmonary vascular bed occurring in disease, e.g., the direct obstruction of the smaller pulmonary vessels in metastatic carcinoma, multiple pulmonary emboli, severe mitral stenosis, and the decrease in the number of smaller vessels seen in chronic pulmonary disease. Inhalation of low oxygen mixtures may reduce the pulmonary vascular bed by vasoconstriction. Any factor tending to increase pulmonary blood flow in the presence of these obstructive lesions tends to raise the pulmonary vascular pressures even more.

In chronic pulmonary disease, pulmonary hypertension usually results from multiple causes. Which of the multiple factors will prevail depends upon the nature of the disease present. The duration and severity of the changes determines whether or not clinical cor pulmonale will result. Reduction in cardiac output and increased pulmonary vascular pressures are the two major physiologic defects characterizing mitral stenosis. These are caused by the valvular deformity, alteration of the pulmonary vascular bed and myocardial disease associated with mitral stenosis. The latter factors also cause congestive heart failure and cardiac arrhythmias. There is no definite relationship between pulmonary blood pressure and cardiac enlargement or cardiac failure. The symptom of dyspnea in these patients cannot readily be accounted for. Recent studies indicate that dyspnea in these patients does not arise primarily from an interference in pulmonary function secondary to pulmonary congestion. The author discusses other possible causes of dyspnea, but the final answer is as yet unknown.

SAGALL

PATHOLOGIC PHYSIOLOGY

Schecter, M. M.: The Superior Vena Cava Syndrome. Am. J. M. Sc. **227:** 46 (Jan.), 1954.

Interference with the return flow of blood through the superior vena cava to the right heart produces (a) increased venous pressure in the upper extremities and thorax, (b) delayed circulation time in the upper part of the body and (c) signs of collateral venous flow toward the inferior caval tributaries. These manifestations can readily be observed and examined by appropriate methods. By the use of phlebography, the precise location of the obstruction and information concerning its nature can be obtained. During the determination of the venous pressure in the upper extremities, an abnormal rise in pressure will be observed if the patient exercises by clenching his hand repeatedly for one minute. By these means, the author has found 22 cases of superior caval syndrome in recent years. The principal cause for this disorder has been the

invasion of the vena cava by malignant tumors. An 11 per cent incidence of involvement of this structure in primary carcinoma of the lung was found. Aneurysm of the ascending aorta represents a less commonly occurring cause owing to its decreasing incidence.

SHUMAN

Hackel, D. B., Kinney, T. D., and Goodale, W. T.: Cardiovascular Effects of Pulmonary Embolization in Intact Dogs Studied by Venous Catheterization of the Coronary Sinus. Am. J. Physiol. **176:** 135 (Jan.), 1954.

A suspension of Lycopodium spores injected into the pulmonary artery produced acute pulmonary hypertension. Coronary outflow was unchanged although the pressure in the pulmonary artery was three times that of the control values. Cardiac output and total pulmonary resistance were increased. Although the left ventricular work was increased, there was also an increase in efficiency since left ventricular oxygen use was unchanged.

OPPENHEIMER

Strane, A., Testoni, F., and Filocamo, G.: Endocavitary Oscillography. Cardiologia **24:** 15 (Fasc. 1), 1954.

Examples are presented of oscillographic intracardiac pressure curves recorded in normals as well as in various pathologic conditions by a method developed by Condorelli. The principle of the method consists of air transmission of pressure variations with the help of a modified Franck capsula. The authors claim the following advantages as compared with conventional manometric methods.

The amplitude of all deflections is larger, particularly in atrial tracings. Artefacts inherent in manometric methods are largely eliminated, and the tracings retain their original contour regardless of the duration of registration. The elimination of the important factor of friction of a liquid column in a narrow tube permits more precise recording of pressure variations. Oscillograms can be easily synchronized with recordings of other manifestations of cardiac activity such as the electrocardiogram, the phonocardiogram and peripheral pulses and thus, a more exact calculation of various phases of the cardiac cycle in the normal and in pathologic states becomes possible.

PICK

Farber, S. J., Alexander, J. D., and Earle, D. P.: Shock Produced by Obstruction of Venous Return to the Heart in the Dog. Am. J. Physiol. **176:** 325 (Feb.), 1954.

When a balloon is inflated in the inferior vena cava above the entrance of the hepatic veins, arterial hypotension is produced. During the hypotension the heart is smaller in size. There is also venous and arterial unsaturation, hemoconcentration, high plasma potassium, decreased urine flow, decreased excretion of electrolytes, low glomerular filtration rate and renal plasma flow. When the blood pressure rises after deflation of the balloon, the blood changes quickly disappear and water and electrolyte excretion become normal. Glomerular filtration rate and renal plasma flow are restored slowly. Prolonged hypotension (two hours) causes irreversible shock. Postmortem examination shows ascites and focal liver necrosis. The heart and kidneys are normal.

OPPENHEIMER

Wilhelmj, C. M., Meyers, V. W., Milani, D. P., and McCarthy, H. H.: Effect of Sodium Chloride upon the Blood Pressure of Normal Dogs When Administered during Dietary Stress. Am. J. Physiol. **176:** 86 (Jan.), 1954.

Dogs which had been fasted for a long time were fed a high carbohydrate diet. This is considered to be a severe dietary stress and results in a marked systolic hypertension. If salt is added later, there is no significant change in blood pressure. When salt was given with the diet, two of three dogs had a systolic hypertension and one had a diastolic rise. The systolic elevation in the latter case (simultaneous salt and high carbohydrate diet) was the same as obtained when salt was added to the diet of fed dogs. Only the sustained systolic elevation during salt feeding and the absence of a sudden fall when salt was stopped are attributed by the authors to the preliminary fasting and high carbohydrate diet. Isocaloric horse meat diets lowered the hypertensive levels established previously due to carbohydrate feeding. Salt did not affect this result.

OPPENHEIMER

Rashkind, W. J., Lewis, D. H., Henderson, J. B., Heiman, D. F., and Dietrick, R. B.: Venous Return as Affected by Cardiac Output and Total Peripheral Resistance. Am. J. Physiol. **175:** 415 (Dec.), 1953.

Peripheral resistance was decreased by stimulation of the carotid sinus nerve, acetylcholine, or opening an arteriovenous fistula. Peripheral resistance was increased by stimulation of the central end of the vagus or sciatic nerve, commercial epinephrine, pure *l*-norepinephrine, pure *l*-epinephrine or asphyxia. With but a single exception, venous return and peripheral resistance changed in the same direction. It was suggested that changes in the venous return are produced by active changes in the tone of the postarteriolar blood vessels. The veins are the most likely site of this activity.

OPPENHEIMER

Liebow, A. A.: Some Aspects of Collateral Circulation of the Lung. Bul. N. Y. Academy Med. **30:** 66 (Jan.), 1954.

Extensive expansion of collateral circulation may develop in pulmonary disease. This may involve the arterial or venous circulation or both. Large precapillary communications may develop between branches of the aorta and pulmonary arteries, acting as points of increased resistance to the outflow from the right ventricle. In pulmonary disease these anastomatic vessels may shunt desaturated blood away from the diseased parenchyma, and actually result in a reversal of blood flow in the pulmonary artery. A burden may be placed entirely on the left side of the heart by this arterial collateral flow passing through the pulmonary capillaries. As the venous collateral circulation expands, an increased shunt between the systemic and pulmonary venous system occurs. The flow of blood in the pulmonary veins depends upon the relative pressures in the pulmonary and systemic veins and, therefore, may be in either direction. In cor pulmonale with congestive heart failure, the venous blood is probably reversed (from right to left), thereby adding unoxygenated blood to the systemic arterial circulation.

SAGALL

Keith, J. D., Rowe, R. D., Vlad, P., and O'Hanley, J. H.: Complete Anomalous Pulmonary Venous Drainage. Am. J. Med. **16:** 23 (Jan.), 1954.

The authors review the literature concerning total uncomplicated anomalous pulmonary venous drainage and report 14 additional cases. The main clinical findings in infants and children are lack of clinical cyanosis and failure to thrive. Murmurs may be absent or faint initially. Later, a parasternal systolic murmur between the second and fourth left intercostal spaces becomes increasingly evident. Diastolic murmurs are occasionally heard. A venous hum was audible in the pulmonary area in about one-fourth of the cases and is specific to one particular type.

The radiologic picture varies with the anatomic type. When the pulmonary veins drain into a left superior vena cava, a characteristic mediastinal venous shadow is present except in the first few months of life. Increasing cardiac enlargement after birth is the rule. Lung vascularity is markedly increased. The electrocardiogram shows marked right ventricular hypertrophy with a qR pattern and inverted T waves in the right precordial leads. Cardiac catheterization is of value but has a number of limitations.

The chief diagnostic difficulty lies in separating this anomaly from aortic hypoplasia in infancy and auricular septal defect in older children. Surgical correction of the condition would seem theoretically possible because of the close proximity of the left auricular appendage to the anomalous venous trunk. However, the small waist of the left auricular appendage, the difficulty in making a large enough anastomosis, the small left auricle and ventricle all militate against successful surgery.

HARRIS

Friedberg, C. K., and Edelman, M. H.: The Mechanism of Syncope Associated with Chronic Auricular Fibrillation Without Evidence of Organic Heart Disease. New England J. Med. **249:** 1057 (Dec. 24), 1953.

The authors report the case of a 35 year old male who had had chronic auricular fibrillation for at least 10 years without evidence of organic heart disease and then developed a series of syncopal reactions. Electrocardiograms revealed that the basic rhythm was auricular fibrillation with periods of ventricular asystole up to two seconds duration. Normal sinus rhythm was re-established after a total dose of 3.2 Gm. of quinidine had been given over a two-day period. Maintenance therapy of 0.2 Gm. of quinidine three times daily was effective in continuing normal sinus rhythm up to the time of the last examination (18 months later). During this period the patient had no further episodes of syncope. This patient, during the time that he suffered syncopal reactions, showed mild hypotension during recumbency and extreme hypotension in the upright position. Because the ventricular standstill lasted only up to two seconds and the syncopal reactions did not coincide with the periods of cardiac standstill, and because syncope occurred only in the upright position, the authors believe that the syncope in this case was due to postural hypotension and not to ventricular asystole. The fact that syncope did not occur after conversion to normal sinus rhythm suggests that the syncope and postural hypotension were in some way related to the auricular fibrillation. The mechanism involved in this association is unknown, but it is suggested that the heart in auricular fibrillation may sensitize the neural arc responsible for the vasodepressor type of syncope. This mechanism may not apply to other unstudied episodes of syncope in this patient or in other patients.

SAGALL

Miller, D. R., Fowler, W. S., and Holmholz, F. H.: The Relationship of Arterial Hypoxemia to Disability and to Cor Pulmonale with Congestive Failure in Patients With Chronic Pulmonary Emphysema. Proc. Staff Meet., Mayo Clinic **28:** 737 (Dec.), 1953.

A study was made of 240 patients with chronic diffuse obstructive emphysema. Values for arterial oxygen saturation were recorded by oximetry with the patients at rest, during exercise, and breathing 90 to 95 per cent oxygen. Half of this group maintained normal values for arterial oxygen saturation, even after exercise, to the limit of their tolerance. Twenty-three per cent had hypoxemia at rest. In an additional 27 per cent whose arterial blood was

normally saturated at rest, hypoxemia developed during a standard exercise test.

Although the incidence of hypoxemia was greater in patients with more marked clinical disability, the presence or absence of hypoxemia did not govern the degree of disability in individual cases. There were many patients with hypoxemia who had a fairly good tolerance to exercise and also numerous patients with normal arterial oxygen saturation who had severe exertional dyspnea. This was true on the basis of the clinical history as well as exercise tests in the laboratory. Cor pulmonale with congestive failure, when present, occurred almost exclusively among patients who had either transient or persistent hypoxemia. The incidence was greatest among those patients with persistent hypoxemia. There was only one case of congestive failure and cor pulmonale among 118 patients in whom normal values for arterial oxygen saturation were recorded at rest and exercise. There were 18 instances of congestive right heart failure among 122 patients in whom persistent or transient hypoxemia was demonstrated.

SIMON

Anderson, R. C., and Adams, F. H.: Congenital Paroxysmal Tachycardia. Report of a Case and Review of the Literature. J. Pediat. **43:** 668 (Dec.), 1953.

A case of congenital auricular flutter was described and a review made of the nine previously described cases of congenital paroxysmal tachycardia. The prognosis is uniformly good with all cases showing a reversion to normal rhythm. Only one case was associated with a known heart defect. Recommended drug treatment is digitoxin in a dosage of 0.06 mg. per 1.0 Kg. of body weight. In cases where the obstetrician is able to diagnose a fetal paroxysmal tachycardia, there would seem to be no good reason for altering the usual management of labor and delivery. Congenital paroxysmal tachycardia differs from that commencing in the early months of infancy by its equal occurrence in males and females and by the preponderance of flutter arrhythmias.

MAXWELL

Brewster, W. R., Jr., Isaacs, J. P., and Wain-Andersen, T.: Depressant Effect of Ether on Myocardium of the Dog and Its Modification by Reflex Release of Epinephrine and Nor-Epinephrine. Am. J. Physiol. **175:** 399 (Dec.), 1953.

In these experiments, ether is demonstrated to have a negative inotropic action on the myocardium. This is sufficient to reduce cardiac output or produce cardiac arrest at blood ether levels required in surgical anesthesia. These cardiac effects of ether take place in the absence of circulating epinephrine and norepinephrine. The reflex release of epinephrine and norepinephrine from the adrenal medulla and sympathetic nerve ends is a major factor of safety in ether anesthesia when myocardial effects are considered. The positive inotropic effects of epinephrine and norepinephrine offset the negative inotropic effect of ether.

OPPENHEIMER

Sunahara, F. A., and Beck, L.: Cardiovascular Effects of Acutely Produced Anemia in the Normal Dog. Am. J. Physiol. **176:** 139 (Jan.), 1954.

An isovolemic anemia was produced in anesthetized dogs. At a critical level of anemia, a further decrease in hematocrit produced a proportional increase in minute volume. Right atrial pressure was unchanged or decreased. After the hematocrit returned to normal, cardiac output decreased without change in atrial pressures. The authors conclude that the arterial-oxygen content is the primary factor in the regulation of the cardiac output.

OPPENHEIMER

Wasserman, K., and Mayerson H. S.: Relative Importance of Dextran Molecular Size in Plasma Volume Expansion. Am. J. Physiol. **176:** 104 (Jan.), 1954.

These experiments demonstrate that plasma expansion is optimal when bled animals receive fractions which are not excreted by the kidney. These same solutions are not so efficient in dogs which have not been bled. Although "Expandex" increases volume in both bled and unbled animals, the expansion is not well maintained; nonrenal-excretable fractions are better. The kidney eliminates the renal-excretable fraction and plasma volume is little increased. Dextran does not change plasma proteins in bled dogs but lowers them in unbled animals. The thoracic duct lymph contained all fractions of Dextran. Renal-excretable and non-excretable fraction increase the lymph flow in unbled dogs. The authors deduce that nonrenal-excretable dextran fraction is better in bled dogs because the larger molecules are retained in the plasma. Small molecules of renal-excretable fraction are lost rapidly into tissue fluids and via the kidney.

OPPENHEIMER

Burch, G. E., and Romney, R. B.: Functional Anatomy and "Throttle Valve" Action of the Pulmonary Veins. Am. Heart J. **47:** 58 (Jan.), 1954.

A study of the anatomy of the pulmonary veins was made on five patients from specimens obtained within three hours after death. Strips, 3 to 5 mm. wide and 35 to 40 mm. long, were cut, beginning from the severed end of the pulmonary vein within the lung and continuing well into the left atrial wall. The strips represented longitudinal segments of vein and segments of left atrium, including the

junctional area. The functional anatomy of this area was studied because of the probable importance of the pulmonary veins in the regulation of pulmonary blood flow and the possibility of spasm of the pulmonary veins as a cause of pulmonary edema.

The smooth muscle of the vein and the atrial myocardium were found to overlap, although it was not always possible to estimate the degree of overlapping. The overlap occurred in two ways: (1) a simple overlap of the atrial myocardium over and external to the smooth muscle of the vein: (2) the atrial myocardium wedged into the smooth muscle layer of the venous wall, being surrounded on both sides with smooth muscle. Grossly, the atrial myocardium seemed to extend onto the pulmonary veins for about 10 mm. In most subjects, the pulmonary veins tended to run perpendicularly into the surface of the atrium. Many nerve fibers were found distributed throughout the walls of the pulmonary vein.

The authors discuss the probable significance of this region in cardiac and pulmonary hemodynamics, and the possible role of the "throttle valve" action of pulmonary veins in acute pulmonary edema, syncope, and sudden death, as well as its therapeutic implications.

RINZLER

Doriee, H., and Goltner, E.: The Effect of Strophantin on Plasma Electrolytes, and Water and Electrolyte Excretion by the Kidney in Normals. Klin. Wchnschr. **32:** 165 (Feb.), 1954.

The effect of intravenous injection of 0.35 mg. of K-strophanthin (Kombetin Boehringer) upon water and electrolyte urinary excretion, and sodium, potassium and calcium plasma levels was studied in 23 normal females. While renal water excretion remained unaffected, excretion of the three electrolytes increased significantly. The authors attribute this to a decrease of tubular reabsorption caused by a direct effect of the glycoside upon the tubular epithelium. Plasma electrolyte concentration also changed to a marked degree following the strophanthin injection. Sodium concentration decreased, potassium increased, while calcium remained unaffected. These alterations suggest a primary shift of potassium out of the cell, while the loss of sodium might be caused by simultaneous transfer of this ion into the cell and excretion through the kidney.

The significance of these findings is discussed with reference to the reduction of plasma volume following injection of strophanthin, and the hyponatremia frequently encountered in the presence of heart failure.

PICK

Fowler, W. S., Helmholz, F. H., Jr., and Miller, R. D.: Treatment of Pulmonary Emphysema with Aerosolized Bronchodilator Drugs and Intermittent Positive-Pressure Breathing. Proc. Staff Meet., Mayo Clinic. **28:** 743 (Dec.), 1953.

A study of 41 patients with chronic diffuse obstructive emphysema was made to evaluate the relative therapeutic merits over a two- to 3-week period of inspiratory positive-pressure breathing of oxygen, inhalation of an oxygen-generated aerosol of isopropyl Arterenol (Isuprel) and their combination. The results, judged chiefly by symptomatic improvement and by results of various pulmonary function tests, indicate that aerosolized Isuprel was superior to oxygen-intermittent positive pressure breathing alone and equal to the combined treatment, including Isuprel aerosol and intermittent positive pressure breathing. Moderate symptomatic improvement was obtained by the majority of patients when an oxygen-generated Isuprel aerosol was administered either with or without intermittent positive pressure breathing. The persistence of dyspnea, although variably reduced, and the unchanged results of pulmonary function tests indicate that the basic bronchopulmonary changes were not altered by any of the treatments given.

SIMON

PATHOLOGY

Edwards, J. E., Parkin, T. W., and Burchell, H. B.: Recurrent Hemoptysis and Necrotizing Pulmonary Alveolitis in a Patient with Acute Glomerulonephritis and Periarteritis Nodosa. Proc. Staff Meet., Mayo Clinic. **29:** 193 (April), 1954.

A case is presented in which recurrent hemoptysis dominated the terminal phase of a clinical picture and in which death resulted from extensive pulmonary hemorrhage. The lungs were shown to be the site of a necrotizing alveolitis, and there were associated acute nephritis and periarteritis nodosa, although no arterial lesions were identified in the lungs. The pulmonary alveolar lesions are interpreted as resulting from a hypersensitivity state. The case emphasizes the point that occasionally recurrent and severe hemoptysis may dominate the clinical picture in a patient with a hypersensitivity state.

SIMON

Longino, L. A., and Meeker, I. A.: Primary Cardiac Tumors in Infancy. J. Pediat. **43:** 724 (Dec.), 1953.

A case is described of primary cardiac tumor in a 3 month old infant, with improvement following surgical drainage of the pericardial sac but followed by death due to spread of the tumor. The most common types of primary cardiac tumors found in early life and the diagnosis and management of infants with such lesions are reviewed.

Infants with primary cardiac tumors often are considered entirely normal at birth with no evi-

dence of cardiomegaly, tracheal or esophageal obstruction, or cyanosis. Subsequently, as the tumor proliferates in an intra- or extracardiac direction, signs of irritability, failure to gain weight, coughing, respiratory retraction, cyanosis, cardiomegaly, and, ultimately, cardiac failure intervene. In the face of such a history, the possibility of a primary cardiac tumor should always be considered, despite its statistical rarity. Surgical intervention is usually of no avail, but perhaps earlier and more frequent recognition of this condition will permit cures to be achieved in those patients having benign tumors or cardiac neoplasms of low-grade malignancy.

MAXWELL

PHARMACOLOGY

Mann, G., Farnsworth, D., and Stare, F.: An Evaluation of The Influence of DL-methionine Treatment on the Serum Lipids of Adult American Males. New England J. Med. **249:** 1018 (Dec. 17), 1953.

Twenty-four adult males, with a blood level of 50 mg. per 100 cc. or more of the S_f 12–20 class of lipoprotein, were given six 0.5 Gm. capsules of dl-methionine daily, by mouth, for 42 days. Their daily routine of activities and diet was not changed. The serum cholesterol and lipoprotein levels were not altered with this course of treatment.

SAGALL

Hackel, D. B., Goodale, W. T., and Kleinerman, J.: Effects of Thiamine Deficiency on Myocardial Metabolism in Intact Dogs. Am. Heart J. **46:** 883 (Dec.), 1953.

Thiamine-deficient dogs (both acute and chronic) demonstrate an abnormal pattern of myocardial metabolism. The coronary arteriovenous difference and total utilization of pyruvate were maintained within normal limits despite markedly elevated arterial pyruvate. The threshold of utilization of pyruvate was significantly increased and the coefficient of extraction was decreased. Lactate extraction was inhibited more than pyruvate; glucose extraction by the myocardium was also below normal. An abnormality in oxygen utilization was demonstrated by the limitation placed on the myocardial oxygen extraction coefficient by higher rates of coronary flow in acute thiamine deficiency.

RINZLER

SURGERY

Kirklin, J. W., Waugh, J. M., Grindlay, J. H., Openshaw, C. R., and Allen, E. V.: Surgical Treatment of Arteriosclerotic Aneurysms of the Abdominal Aorta. Arch. Surg. **67:** 632 (Nov.), 1953.

The authors described their experiences with surgical treatment of 23 patients suffering from aneurysms of the abdominal aorta. Thromboendarterectomy was performed in four cases and resection and replacement by aortic graft were utilized in one case. In the remaining 18 patients, reinforcement with polyvinyl sponge was carried out. Of the latter group, two died. One of the four patients in whom thromboendarterectomy was performed also died, while in another, arterial insufficiency developed in one lower extremity, necessitating a mid-thigh amputation.

Follow-up studies revealed that 5 of the 15 patients surviving reinforcement of the abdominal aneurysm with polyvinyl sponge subsequently died as a result of the disease, while another patient, although still alive, suffered from constant, severe and progressing pain. Of the three patients who survived thromboendarterectomy, two were alive and asymptomatic, while one died suddenly seven months after operation.

It was the opinion of the authors that the procedures utilized did not significantly increase the survival rate as compared with a series of untreated patients. They concluded that possibly the best approach to the problem was through the use of preserved homologous aortic grafts.

ABRAMSON

Gross, R. E., and Watkins, E., Jr.: Surgical Closure of Atrial Septal Defects. Arch. Surg. **67:** 670 (Nov.), 1953.

Surgical considerations and various methods for closing atrial septal defects are discussed by the authors with suitable comments and criticisms. Their own methods for handling the various types of interauricular septal defects are presented. For posterior defects, which are neither very high nor very low in the septum, the authors found it amazingly easy to obtain closure by drawing the septal edge back to the posterior wall of the auricle with mattress sutures. This procedure was carried out by passing a finger into an auricle through the appendage, effectively and thoroughly closing the septal orifice, withdrawing the finger and suturing the auricular appendage, all in less than 10 minutes.

For those lesions which may be very high, very low or very far forward, and for all of the openings which are great in size, a rubber "well" can be attached to the opened auricle, forming a pool of blood through which the fingers can be passed into the auricular chamber, allowing by tactile direction with the fingers a repair of the septal opening by direct suture or by the onlay of a polyethylene sheet which is made to cover the opening. This foreign material, from observations on dogs, has been found to be tolerated very well and is known to become covered over with fibrous tissue and endocardium.

The authors point out that many patients with atrial septal defects have anomalous drainage of the pulmonary veins, particularly of those veins from the right lung. Fortunately, most anomalies of pulmonary vein drainage are such that the vessels enter the right auricle. In this situation, repair is

done in such a way that all pulmonary vein blood is directed into the left auricle, as well as abolishing the communication between the two auricles.

The authors report on the use of the two main technics in 12 patients. There have been seven survivors. In four of these the septum was repaired by direct suture; in three others the opening was closed by the onlay of a polyethylene sheet which was sewed into place and anchored to the septum. It is pointed out that small interauricular shunts can be tolerated by the human heart through a long life and, hence, do not require any surgical relief. Large interauricular shunts in which the pulmonary blood flow is twice (or more) that of the peripheral blood flow should be subjected to surgical closure of the septal opening.

DENNISON

Black, S. P. W., and German, W. J.: The Treatment of Internal Carotid Artery Aneurysms by Proximal Arterial Ligation. A Follow-Up Study. J. Neurosurgery **10:** 590 (Nov.), 1953.

Aneurysms of the internal carotid artery, both in the cavernous and cerebral portions, have been treated in this clinic for the past 16 years by proximal arterial ligation in the neck. Thirty-five patients are presented in this series. To date, eight patients have died of various causes and 27 are living. The usual site of ligation in patients over 40 years of age was the common carotid. In some instances the internal carotid was subsequently ligated. In younger patients, the internal was ligated initially unless there was evidence of existing or impending vascular deficit as determined clinically and by intra-arterial pressure determination at the time of ligation.

The therapeutic objective is simple: to reduce strain on the aneurysm while maintaining adequate circulation to all parts of the brain. Strain upon the aneurysm is equal to the sum of the stresses operating. These include: total hydrostatic pressure in the parent artery; the pulsatile nature of the flow; turbulence; and jet action.

The authors do not advocate ligation in the neck for aneurysms of arteries other than the carotid, especially of the communicating series. While the principle of proximal ligation for intracranial aneurysms is validated largely on an empiric basis, this study would tend to indicate that the procedure has a sound theoretic basis. The authors feel that most of the patients in this series have been benefited by the procedure, but the percentage gain in terms of morbidity and mortality can be assessed only in relation to comparable series of untreated cases.

DENNISON

Butterworth, J. S.: Abnormal Rhythms Associated With Cardiac Surgery and Their Treatment. Ann. Int. Med. **39:** 1088 (Nov.), 1953.

The arrhythmias which can occur during cardiac surgery include paroxysmal supraventricular tachycardia, auricular fibrillation, auricular flutter, isolated ventricular premature contractions, ventricular tachycardia and ventricular fibrillation. Of these, ventricular tachycardia and ventricular fibrillation constitute the most serious types of arrhythmia. The latter demands immediate heroic treatment by a trained team making use of the defibrillator, followed by mechanical massage and intracardiac injections of calcium chloride and/or epinephrine. Ventricular tachycardia can be treated by intravenous injection of either pronestyl or quinidine. The supraventricular tachycardias can be controlled by prostigmine or Tensilon. Paroxysmal auricular fibrillation or flutter can be treated with either digitalis, quinidine, or pronestyl. As yet, there are no dependable means for preventing the arrhythmias which occur during cardiac surgery, so that the anesthesiologist and the surgeon should be alerted to their possible development and be prepared to treat this complication immediately.

WENDKOS

Shaw, K. M.: Right-Sided Thoracic Approach for Combined Lobectomy and Mitral Valvotomy. Lancet **6796:** 1130 (Nov. 28), 1953.

A patient with carcinoma of the lower lobe of the right lung and mitral stenosis was improved by a combined lobectomy and mitral valvotomy, using a right-sided thoracic approach. The valvotomy was accomplished by finger-pressure through the right inferior pulmonary vein following the lobectomy.

MAXWELL

Thomas, W. A., Averill, J. H., Castleman, B., and Bland, E. F.: The Significance of Aschoff Bodies in the Left Atrial Appendage. A Comparison of 40 Biopsies Removed During Mitral Commissurotomy with Autopsy Material from 40 Patients Dying with Fulminating Rheumatic Fever. New England J. Med. **249:** 761 (Nov. 5), 1953.

Of 40 patients subjected to surgery for mitral stenosis, Aschoff bodies were found in the surgical specimens of 55 per cent. Less than half of this group had a past history of rheumatic fever and none had had evidence of recent rheumatic activity. The atrial appendages of 40 patients who died with severe fulminating rheumatic fever were examined for comparison. The endocardium of the atrial appendages in all of these cases showed striking pathologic changes. Seventy-two per cent showed one or more Aschoff bodies, and 95 per cent showed infiltration with lymphocytes and monocytes. Myocardial changes were less prominent with only two patients showing Aschoff bodies. There was a close correlation between the pathologic findings in the atrial appendages and those found in routine sections from other portions of the heart. These findings indicate that latent rheumatic activity, although not apparent clinically, was present in the surgical group.

The postoperative courses of 25 per cent of patients with prolonged convalescence, low grade fever, tachycardia, friction rubs, pneumonitis, arrhythmias, atypical chest pain, or arthritis would seem to substantiate this belief. Aschoff bodies were not found in nine patients over 50 years of age who had valvular lesions consistent with inactive healed rheumatic endocarditis and in a group of 50 persons who died from other causes and had no gross anatomic evidence of rheumatic heart disease.

SAGALL

THROMBOEMBOLIC PHENOMENA

Dencker, S. J.: Studies in Artificial Peripheral Embolism in the Rabbit. Scaninav. J. Clin. & Lab. Invest. **5:** 261, 1953.

Using rabbits, the author studied various means of preventing experimentally produced emboli from occluding cerebral arteries. It was found that where no measures were used, 27 per cent of the animals demonstrated emboli in these vessels. Ligation of the left carotid artery did not increase the risk of cerebral embolization on the other side, while maintenance of the head in a raised position or manual compression of both carotid arteries diminished the incidence of this state. A combination of these two measures further reduced the possibility of cerebral embolization. The possible clinical implications of such findings were presented.

ABRAMSON

VASCULAR DISEASE

Schettler, G., and Dietrich, F.: The Significance of Xanthoma and Xanthelasma in Atherosclerosis. Klin. Wchnschr. **31:** 1040 (Nov.), 1953.

The authors reviewed the literature on lipoidosis and studied in their own material the incidence of atherosclerosis in various types of primary and secondary disturbances of lipoid metabolism.

Essential familial hyper*cholesteremic* xanthomatosis is, in a high percentage of cases, associated with general and coronary arteriosclerosis. The majority of juvenile arteriosclerotic patients belong to this group. In contrast, patients with essential familial hyper*lipemic* xanthomatosis remain practically free from arteriosclerosis even with persistence of the metabolic disorder for many years. Secondary hypercholesteremic xanthomatous diseases may be caused by a variety of conditions. If associated with primary biliary cirrhosis of the liver the incidence of atheromatosis is very low. Xanthomatous skin lesions occurring in diabetes mellitus, in pancreatic disease and in cholecystopathies appear to be unrelated to arteriosclerotic vascular disease.

PICK

Knowles, H. C., Jr., Zeek, P. M., and Blankenhorn, H. A.: Studies on Necrotizing Angiitis. Arch. Int. Med. **92:** 789 (Dec.), 1953.

Thirty-five cases of periarteritis nodosa and 10 cases of hypersensitivity angiitis are reviewed and tabulated. Certain striking differences in course and symptomatology have been revealed. In the 14 cases designated primary periarteritis nodosa, there were widespread lesions in various stages at necropsy after a long clinical course characterized by gastroenteric symptoms, peripheral neuropathy, hypertension, and occasionally, eosinophilia. Twenty-one cases of secondary periarteritis nodosa were essentially cases of renal disease with hypertension, in which a few lesions of periarteritis nodosa had been initiated a short time before death. In these the clinical findings of periarteritis nodosa were masked by those of severe renal disease and hypertension.

In sharp contrast, in the 10 cases of hypersensitivity angiitis, the clinical manifestations were of a fulminating disease characterized by fever, skin rash, nephritis, myocarditis, and frequently a history of recent sulfonamide ingestion. It is concluded that periarteritis nodosa and hypersensitivity angiitis can be differentiated clinically, and represent two distinct disease conditions.

BERNSTEIN

Kampmeier, R. H., and Shapiro, J. L.: Diffuse and Sometimes Recurrent Course of Diffuse Arteritis. Arch. Int. Med. **92:** 856 (Dec.), 1953.

The cases which have been considered show the variability of the clinical course of diffuse arteritis. Rapidly progressing necrotizing arterial disease, leading to fatal termination, may occur if the arteritis is of acute onset, representing a generalized insult to the vascular system. If the process is a recurring one with remissions and exacerbations, the pathologic change may vary from acute necrosis to healing with recanalization.

The course of a disease characterized by diffuse arteritis and extending over a period of more than 20 years is presented. Remissions and exacerbations were present, and there is proof that arterial disease of varying degrees and types was present during this period. Biopsy studies emphasize the focal nature of the arteritis under discussion since numerous sections are often needed to demonstrate the essential lesions. Because of its great variability, the clinical course might well have been classified as dermatomyositis upon one occasion, as disseminated lupus erythematosus on another occasion, and as periarteritis nodosa on still another occasion. In fact the great variety of manifestations of disease throughout a period of over 20 years precludes its designation as any single type of arteritis now classified.

BERNSTEIN

Heyman, A., Patterson, J. L., Jr., Duke, T. W., and Battey, L. L.: The Cerebral Circulation and Metabolism in Arteriosclerotic and Hypertensive

Cerebrovascular Disease with Observations on the Effects of Inhalation of Different Concentrations of Oxygen. New England J. Med. **249:** 223 (Aug. 6), 1953.

This report is concerned with observations of cerebral blood flow and metabolism in 48 control subjects of varying ages, and 39 patients with cerebrovascular accidents or with encephalomalacia associated with arteriosclerosis and hypertension. The effects of inhalation of 50 and 100 per cent concentrations of oxygen were also studied. The cerebral blood flow was somewhat lower in older control subjects than that in young, healthy subjects, and it was even more greatly reduced in patients with cerebrovascular accidents. There was also a marked reduction of the cerebral oxygen consumption in patients with chronic cerebrovascular disease. In patients with an acute cerebrovascular accident, the mean cerebral oxygen consumption was only slightly lower than that of the older control group. Inhalation of 85 to 100 per cent oxygen produced an increase in cerebral vascular resistance and a decrease in cerebral blood flow in all patients. Inhalation of 50 per cent oxygen concentrations produced similar but less striking changes. The uptake of oxygen by the brain was unaffected by either concentration. It is suggested that, in view of the vasoconstrictive effects of 100 per cent oxygen shown by these studies, it would seem wise to avoid administration of 100 per cent oxygen by mask in patients with cerebral vascular disease and to use a nasal catheter or tent which supply concentrations of approximately 35 to 50 per cent oxygen.

ROSENBAUM

Berkman, J., Rifkin, H., and Ross, G.: The Serum Polysaccharides in Diabetic Patients with and without Degenerative Vascular Disease. J. Clin. Investigation **32:** 415 (May), 1953.

A study was made of certain polysaccharide components in the sera of 66 diabetic patients with and without clinically detectable degenerative vascular disease. The concentration of total nonglucosamine polysaccharides bound to serum protein, serum glucosamine and the protein (tyrosine) and polysaccharide of serum mucoprotein were found to be within normal limits in those patients without degenerative vascular disease. However, those with such changes manifested an increase in the total polysaccharides bound to serum proteins and glucosamine of the serum. No constant relationship was noted between the level of blood sugar and the concentration of the various serum polysaccharide substances measured.

It was concluded that the increased concentration of the polysaccharides reflected the widespread degenerative alterations in blood vessels and other structures.

ABRAMSON

Lundback, K.: Diabetic Angiopathy. A Specific Vascular Disease. Lancet **1:** 377 (Feb. 20), 1954.

The basis for the author's conviction that diabetic angiopathy is a specific entity distinct from arteriosclerosis and from atherosclerosis is as follows. The male-female ratio is one. The ophthalmoscopic findings are specific. The histologic findings in the kidney are specific. There is an alleged difference in the lipid fractions extractable from the coronary arteries of diabetics. In diabetics, serum concentrations of phospholipid and cholesterol rise in a parallel fashion so that the ratio remains normal. The author insists that the conception of the vascular disease in diabetes as a distinct entity will hasten elucidation of its pathogenesis.

MCKUSICK

Dock, W.: Atherosclerosis—Inevitable or Controllable? Canad. M.A.J. **69:** 355 (Oct.), 1953.

Atherosclerosis in North Americans begins in early infancy and the rate of lipid deposition shows three peaks, the highest in the first year of life, with lower peaks in early adolescence and early middle age. The process depends on inability of most human beings to deal with the modern high fat, high cholesterol diet. In animals very rapid atherosclerosis can be produced, even in immature individuals, by high cholesterol intake; high fat diets or fattening on carbohydrate has not been shown to lead to atherosclerosis in men or animals on low cholesterol diets with good protein content. Men with coronary disease early in life are no more obese than controls still free of symptoms.

Cholesterol reabsorption can be blocked by other sterols, which in themselves are not absorbed. This suggests the possibility of control by dietary supplement rather than restriction. At present, a low fat, low cholesterol diet is reasonable for those with precocious onset of arteriosclerosis, but the protein content should be liberal. Should it be proved that man, unlike other animals, is uneffected by excess cholesterol feeding, and his vascular disease is a result of the excess fat, the outlook for control is bleak. It would involve a change in diet, from early childhood on, which the population would never accept.

BERNSTEIN

Shnider, B. I., and Cotsonas, N. J., Jr.: Embolic Mycotic Aneurysms, A Complication of Bacterial Endocarditis. Am. J. Med. **16:** 246 (Feb.), 1954.

The authors present two illustrative proven cases and one probable case of embolic mycotic aneurysm complicating bacterial endocarditis and review 59 additional cases reported since the last complete report in 1923. The development of an embolic mycotic aneurysm is an unusual but serious complication of bacterial endocarditis. Four characteristic clinical syndromes are described which allow

for recognition or a high index of suspicion. These syndromes reflect the intracranial, abdominal, thoracic or peripheral extremity location of the mycotic aneurysm.

HARRIS

Ressler, N., Bogle, A. J., and Kosai, M.: The Relation of Serum Stability to the Development of Arteriosclerosis. Am. J. Clin. Path. **24:** 194 (Feb.), 1954.

A study of the colloid stability of the serum was made in 133 patients with arteriosclerosis, 60 normal individuals, and 13 patients with various diseases but free of stigmata of arteriosclerosis. Colloid stability of serum depends upon the charge of the protein molecules. By adding cations under standard set conditions, the negative charge is decreased and coalescence of protein occurs with resultant turbidity. The rate of development of turbidity can be measured. Colloid stability of serum is decreased specifically by addition of gamma globulins, cholesterol, and decrease in pH. Acute disease processes can alter the factors controlling colloid stability of serum. Thus in patients with arteriosclerosis, and in patients with other acute disease processes, the serum stability was lowered in 90 per cent by addition of metallic cations to the serum. It is theorized then that the deposition of cholesterol and of calcium upon vessel walls is aided by the decrease in the colloid stability of the "blood transudate" as it passes through the arterial intima.

HARVEY

OTHER SUBJECTS

Tagnon, H. J.: Enzymes in Clinical Medicine. Recent Developments in the Practical Application of Enzymes to Clinical Medicine. New England J. Med. **249:** 650 (Oct. 15), 1953.

With few exceptions, every chemical reaction occurring in the cells of the organism is catalyzed by enzymes. The study and recognition of deranged metabolism or disease is therefore largely based on enzymology. Enzymes are organic catalysts which differ from other catalysts in that each enzyme catalyzes only one kind of reaction. Because enzymes are protein and derived from animal tissues, the problem of antigenicity has to be overcome if prolonged administration is to be undertaken. Attempts at using enzymes therapeutically have become possible only since purified and crystalline enzymes have become available. The majority of enzymes are intracellular and their site of action is in the cytoplasm of the cell. To be effective, penetration of the enzyme into the cell after therapeutic administration becomes necessary. If enzymes could traverse the cell membrane, it is improbable, at present, that they would reach the precise intracellular location where they could exert their activity. Many enzymes require cofactors or coenzymes for their activity, and to be therapeutically active such an enzyme given parenterally would require an adequate concentration of cofactors at the intended site of action. Recent uses of enzymes have been confined to those which do not require cofactors and they have been employed for actions which do not require penetration of the enzyme into the cell. These enzymes have belonged to the peptidases.

Streptococci elaborate two enzymes. One of these streptokinase, activates proplasmin into the active proteolytic enzyme of plasma (plasmin). The other enzyme is streptodornase, whose substrate is desoxyribonucleoprotein. These two enzymes have been used for the liquefaction of purulent and hemorrhagic exudates in closed cavities, amebic abscess, unresolved pneumonia and similar situations, making adequate drainage possible. These enzymes are definitely antigenic and antibodies usually develop after a period of about two weeks, persisting up to three months after cessation of therapy. The application of these enzymes to wounds, burns and ulcers to achieve a type of medical débridement has also been developed. The objective is limited to cleansing. Unfavorable reactions have been reported in lesions due to irradiation. To obtain an adequate result, there must be proper contact between the enzyme and the surface to be cleaned.

Theoretically, streptokinase, an activator of plasmogen, should be of value in stimulating increased production of plasmin which would remove fibrin when abnormal clotting is present. However, it has been found that to accomplish this intravenous injection of adequate amounts of streptokinase is pyrogenic. Although intravenous injection of trypsin reduces the level of fibrinogen and prothrombin in the circulating blood, small doses of this proteolytic enzyme hasten blood coagulation in vivo as well as in vitro. Blood plasma is also a powerful trypsin inhibitor, and the small amounts of trypsin that are nontoxic, which have been given intravenously for the treatment of thromboembolic diseases, are probably ineffective because they are completely neutralized by the serum inhibitor. The author recommends an attitude of extreme caution in the intravenous use of trypsin in humans. Chymotrypsin has no clotting activity on blood and is generally less toxic than trypsin. However, experiments with this enzyme upon preformed clots in animals have not been impressive. The enzyme plasmin, prepared from human plasma, is another material which may hold promise in thromboembolic disease.

Measurement of acid phosphatase of the serum and of serum cholinesterase are examples of the diagnostic application of measurements of enzymes or enzyme inhibitors. A prostatic fibrinolysin has been found in a small proportion of patients with

metastatic carcinoma of the prostate. There is evidence that proteolytic activity may appear in the blood in certain disorders such as shock due to trauma, hemorrhages or burns, liver disease, cancer of the prostate, and possibly extensive surgical procedures associated with transient anoxemia. This fibrinolysis is believed to cause fibrinogenopenia. When fibrinolysis is intense, it produces a hemorrhagic condition with deficiency of prothrombin, accelerator globulin and fibrinogen, and weak, fragile clots.

ROSENBAUM

Schnur, S.: Mortality Rates in Acute Myocardial Infarction. II. A Proposed Method for Measuring Quantitatively Severity of Illness on Admission to the Hospital. Ann. Int. Med. **39:** 1018 (Nov.), 1953.

A method for estimating quantitatively the severity of illness of patients with acute myocardial infarction on admission to the hospital was accomplished by devising a scoring system termed "Pathologic Index Rating." The determinants in computing the Pathologic Index include the following: (1) shock, (2) heart failure, (3) arrhythmia, (4) gallop rhythm, (5) preceding history of heart or vascular disease, (6) associated serious diseases. A numerical value is assigned to each of these determinants and the Pathologic Index computed on their sum in any individual case. Such a Pathologic Index Rating was found to be closely related to the mortality rate, ranging from 8 per cent in the group with the lowest rating to 95 per cent in the group with the highest rating. In attempting to evaluate the results of any therapeutic procedure this method could be useful in the design of a controlled experiment, the patients being paired on the basis of their pathologic index, and then alternately assigned to the treated and untreated groups. This approach would seem to be superior to past practices in establishing the merits of any therapeutic program in lowering mortality and morbidity in myocardial infarction.

WENDKOS

Goyette, E. M.: Acute Idiopathic Pericarditis. Ann. Int. Med. **39:** 1032 (Nov.), 1953.

The clinical and laboratory features of 28 cases of acute benign pericarditis encountered over a three and one-half year period at Fitzsimons Army Hospital are summarized. The findings are in accord with those noted in previous publications dealing with this disorder. The differentiation of this condition from acute myocardial infarction is stressed. Emphasis is placed upon a proper evaluation of the electrocardiographic findings, particularly in serial records. Treatment is symptomatic and should not include the use of anticoagulants. Antibiotics have no proven benefits.

WENDKOS

Hamilton, W. F., Ellison, R. G., Pickering, R. W., Hague, E. E., and Rucker, J. T.: Hemodynamic and Endocrine Responses to Experimental Mitral Stenosis. Am. J. Physiol. **176:** 445, (March), 1954.

Mitral stenosis was produced gradually in dogs by ligation of the mitral orifices. The resulting murmur was typical. Pulmonary blood pressure is increased. These animals are susceptible to hypoventilation. There is sodium retention and ascites. Para-aminohippurate and creatinine clearances were hardly disturbed. Venous pressure showed little elevation. It is suggested from incomplete endocrine studies that the posterior pituitary and adrenal glands are implicated.

OPPENHEIMER

Yamakawa, K., Shionoya, Y., Nagair, T., Kitamura, K., Ohta, S., and Yamamoto, T.: An Attempt at Intracardiac Phonocardiography. Tohoku J. Exper. Med. **58:** 311 (Oct.), 1953.

Intracardiac phonocardiography, was performed by means of a condenser microphone using the body as one pole. The experiments were carried out on dogs and oscillograms were taken with limb lead or intracardiac unipolar lead electrocardiograms. By this means, a recording was obtained of a distinct vibration which occurred synchronously with the heart sounds that are usually recorded from the chest wall as the auricular, first, second, and third sounds. Moreover, the heart sounds thereby obtained were found to possess the same characteristics as those taken from the chest wall.

The phonocardiogram recorded from the chest wall during this stage did not give distinct tracings of auricular and third sounds. It was at first feared that some artefact might appear on the intracardiac phonocardiogram as a result of the introduction of the catheter into the heart cavity, but no such event occurred when the degree of amplification was suitable.

BERNSTEIN

Cook, D. L., Mills, L. M., and Green, D. M.: The Mechanism of Alloxan Protection in Experimental Atherosclerosis. J. Exper. Med. **2:** 119 (Feb.), 1954.

Experiments were performed to compare the effects of cholesterol feeding in control rabbits, alloxan-diabetic rabbits, and rabbits injected with alloxan while the pancreas was temporarily occluded from the circulation. The alloxan-diabetic rabbits consumed significantly higher quantities of cholesterol and food and had serum cholesterol and lipoprotein (S_f 5–9 and S_f 16–30) concentrations significantly increased over the control levels. They failed to show a commensurate increase in the degree of atherosclerosis.

Rabbits in which the diabetogenic action of al-

loxan was prevented by temporary occlusion of the pancreas from the circulation during its administration developed grades of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis not significantly different from the controls. The results are interpreted as indicating that the effects of alloxan on tissues other than the pancreas do not protect against experimental atherosclerosis produced by cholesterol feeding.

BERNSTEIN

Soloff, L., and Zatuchni, J.: Some Difficulties in Evaluating Functional Results after Mitral Commissurotomy. J.A.M.A. **154:** 673 (Feb. 20), 1954.

Most reports on the so-called functional improvement following mitral commissurotomy have to be taken on faith. The technical accomplishments of this group of blind and crude procedures is interpreted by one individual—the surgeon. To be meaningful, reports attributing improvement to mitral commissurotomy should show that (1) medical and naturally occurring factors were not active and (2) no deleterious effects were produced. Sufficient factual data should be given so the reader can form his own conclusions and the surgeon's conception of his accomplishment should be included. Correlation of these statements with the so-called functional improvement may help to differentiate the psycho-therapeutic, naturally occurring, and medically induced remissions from the surgical accomplishments. This differentiation is extremely important because the operation has an immediate higher mortality (about 6 per cent) than the naturally occurring mortality (about 1 per cent) and its morbidity is very high. The fact that the heart can adjust functionally to the added load imposed on it by surgery should not be permitted to mask the actual effects of the operation.

KITCHELL

MacKinnon, I. L.: Observations of the Pulse Rate During the Human Menstrual Cycle. J. Obst. & Gynec. Brit. Emp. **61:** 109 (Feb.), 1954.

During 22 complete menstrual cycles, daily radial pulse rates and body temperatures were observed on 10 healthy, young, unmarried women between 7:00 a.m. and 8:00 a.m., before they rose from bed. The average pulse rate was faster during the luteal phase than during the follicular phase of the cycle. This pulse rate acceleration was not commensurate with the elevation of body temperature observed. The author postulates that increased corticoid activity during the luteal phase of the cycle is responsible for the failure of the heart rate to accelerate commensurately with the elevation in body temperature.

SAGALL

Millar, W. G.: Pregnancy and Polycystic Disease of the Kidneys. J. Obst. & Gynaec. Brit. Emp. **6:** 868 (Dec.), 1953.

The cases described comprise only a small series of 5 cases, but from a study of these and the cases reported in the literature the following conclusions seem justified according to the author. In the absence of abnormal signs or symptoms, polycystic disease of the kidneys is no contraindication to the continuation of the pregnancy. Urinary infection is frequent, but can usually be satisfactorily controlled by chemotherapy or antibiotics, and pregnancy should be allowed to continue. In the presence of hypertension, the continuation of pregnancy is a hazardous procedure and interruption is advised.

BERNSTEIN

Callagham, J. C., McQueen, D. A., Scott, J. W., and Bigelow, W. G.: Cerebral Effects of Experimental Hypothermia. Arch. Surg. **68:** 208 (Feb.), 1954.

The effects of a low environmental temperature on cerebral tissue were studied in a series of 10 immature monkeys. The animals were placed in an ice-water bath kept at 10 C. All 10 monkeys survived the lowering of the body temperature to 20 C. or less. The heart and respiratory rate was reduced, with deep unconsciousness occurring as cooling progressed. Electroencephalographic studies disclosed a depression of cortical activity during cooling, with little or no activity at 20 C. Subsequent examinations revealed that there was no effect on the aptitude with which the animals performed tests learned prior to the experiment.

It was concluded that in the monkey a reduction of body temperature to 20 C. appeared to have no permanent ill effects on cerebral function.

ABRAMSON

Kvale, W. F.: An Evaluation of Medical and Surgical Treatment of Occlusive Arterial Disease. Proc. Staff Meet., Mayo Clin. **29:** 148 (Mar.), 1954.

It is well to point out that many drugs improve the peripheral arterial circulation in small or great degree and for short or long periods. Continuous long-term therapy with drugs does not appear to be feasible. Surgical sympathectomy remains the method of choice for increasing the circulation to the skin of the extremities. The author prefers surgical sympathectomy to medical treatment except in cases in which the general condition of a patient imposes an undesirable surgical risk and in instances in which the arterial circulation is not sufficiently jeopardized to warrant sympathectomy. Chemical sympathectomy is a useful and justifiable procedure when the risk of a surgical sympathectomy seems to be too great, and when vasodilation is desired for several weeks or months. Drugs are preferable to sympathectomy in acute arterial oc-

clusion. Early diagnosis is important in occlusive arterial disease. The diagnosis ordinarily is not difficult to make. In a few carefully selected cases, arteriography and aortography may be necessary to find the rare, isolated instance of segmental disease of the aorta or major artery. If such an instance is found, appropriate surgery can be performed. If the disease is one of a diffuse nature, then institution of adequate active and prophylactic treatment may do much to prevent pain, disability, gangrene and economic loss.

SIMON

McIlroy, M. B., and Christie, R. V.: The Work of Breathing in Emphysema. Clin. Sc. **13:** 147 (Feb.), 1954.

The work of pulmonary ventilation in patients with emphysema was measured by the authors' previously described method. Compared with normal subjects the work done against nonelastic resistance is greatly increased, and the work done against elastic resistance is relatively diminished. Furthermore, active work is performed during the expiratory phase. Emphysematous patients show an inordinate increase in respiratory work on exercise. For example, a patient with emphysema may have to perform as much work while breathing 15 liters a minute as a normal subject breathing 40 liters a minute. This abnormal increase in respiratory work must be an important factor in accounting for dyspnea and in limiting the maximal breathing capacity. The increase in nonelastic resistance is not wholly due to bronchial obstruction, since there is a comparatively small reduction in resistance upon breathing hydrogen. It is due in part to changes in the viscous properties of the lung itself which are probably irreversible.

ENSELBERG

Cipollaro, A. C., and Schwartz, P.: The Cutaneous Manifestations of Systemic Diseases. New England J. Med. **250:** (Jan. 14), 1954.

It is pointed out that many pathologic states, including those which are metabolic, endocrine, infectious or malignant, frequently manifest themselves first in the skin. The lymphoblastomas are cited as an example, and it is mentioned that the first sign of lymphoblastoma may be severe, intractable pruritus with no visible dermatitis. Mycosis fungoides is eczematous in its early stages, and, if recognized early and treated with superficial x-ray therapy, the life of the patient may be prolonged for many years. Changes appear in the skin in about 40 per cent of cases of leukemia, although chronic myelogenous leukemia is rarely so manifested. However, chloroma is an unusual type of chronic myelogenous leukemia in which skin tumors of greenish hue make their appearance. The so-called lipoidoses may be diagnosed by cutaneous inspection, the primary lesion being a xanthoma, a nodule composed of foam cells. Xanthomas may appear in myxedema, biliary cirrhosis, obstruction of the common bile duct, hemochromatosis, and hereditary xanthomatosis. Xanthoma tuberosum multiplex is often associated with definite involvement of the cardiac valves, coronary and other blood vessels and circulatory impairment which may lead to sudden death. The authors consider xanthelasma of the eyelids an early sign of impending trouble, particularly anginal accidents. Poorly controlled diabetes results in hyperlipemia and xanthoma diabeticorum; it is said that cardiovascular disturbances may follow. Necrobiosis lipoidica diabeticorum is usually accompanied by a familial tendency to peripheral vascular disturbances. The reticuloendothelial diseases which have been reclassified in the eosinophilic granuloma group present various skin manifestations including petechiae, xanthomata, and changes in skin color. The collagen diseases including lupus erythematosus, scleroderma, dermatomyositis and periarteritis nodosa are reviewed. Periarteritis nodosa is said to be seen seldom by dermatologists. The association of dermatitis herpetiformis or very similar skin lesions with a number of systemic disorders is mentioned; these include carcinoma of the liver, cirrhosis, liver disease due to cincophen, retroperitoneal lymphosarcoma, carcinoma of the uterus and pregnancy.

ROSENBAUM

Martin, P.: Phlegmasia Caerulea Dolens. Brit. M. J. **2:** 1351 (Dec. 19), 1953.

This designation is employed by the author for the association of acute ischemia or even gangrene with thrombophlebitis of an extremity. Pseudoembolic phlebitis, blue phlebitis and gangrenous thrombophlebitis are other terms which have been applied. This particular clinical picture is likely to follow abrupt obstruction of the major venous drainage of a limb. It may follow venous ligation. Heparin, heating of the unaffected extremity and heavy sedation are recommended. Paravertebral sympathetic block may be risky in the presence of heparinization.

MCKUSICK

Goldman, M. J., and Lau, F. Y. K.: Acute Pericarditis Associated with Serum Sickness. New England J. Med. **250:** 278 (Feb. 18), 1954.

Two cases of serum sickness following administration of tetanus antitoxin are described. One case is reported in considerable detail. Evidence for pericarditis included transient inverstion of the T waves in leads aV_L, aV_F, V_3, V_4, V_5 and V_6, as well as pericardial friction rub and considerable pain in the chest. A favorable response to cortisone was observed and all abnormalities cleared promptly. It is felt possible that pericarditis or myocarditis or both are more common in this disorder than is recognized clinically.

ROSENBAUM

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Sympathetic Control of Human Blood Vessels. Monographs of Physiological Society, No. I. *H. Barcroft, M.A., M.D., M.R.C.P., and H. J. C. Swan, Ph.D., M.B., B.S., M.R.C.P.*, London, Edward Arnold, Baltimore, Williams & Wilkins, 1953. 165 pages, 77 figures, 9 tables. $3.75.

Sectional Radiography of the Chest. *Irving J. Kane, M.D. Foreword by Edward D. Churchill, M.D.* New York, Springer, 1953. 154 pages, 101 figures. $7.50.

Machinery of the Body, ed. 4. *Anton J. Carlson and Victor Johnson.* Chicago, University of Chicago Press, 1953. 663 pages, 223 figures, 15 tables $5.50.

Clinical Unipolar Electrocardiography, ed. 2. *Bernard S. Lipman, A.B., M.D., and Edward Massie, A.B., M.D., F.A.C.P.* Chicago, Year Book Publishers, 1953. 309 pages, 260 figures. Price, $6.50.

Spatial Vectorcardiography. *George E. Burch, M.D., J. A. Abildskov, M.D., and James A. Cronvich, M.S.* Philadelphia, Lea & Febiger, 1953. 173 pages, 121 illustrations, 19 tables. $5.00.

Hypertensive Diseases. Causes and Control. *Henry A. Schroeder, M.D., F.A.C.P. With Contributions by Gregory S. Gressel, M.D., Dean F. Davies, Ph.D., M.D., H. Mitchell Perry, Jr., M.D., and Donald F. Gibbs, M.B., Ch.B., M.R.C.P., (Edin.).* Philadelphia, Lea & Febiger, 1953. 610 pages, 164 figures, 3 color plates, 106 tables. $10.00.

Physiological Cardiology. American Lecture Series in Physiology. *Arthur Ruskin, M.D., F.A.C.P.* Springfield, Ill., Charles C Thomas, 1953. 370 pages, 9 figures, 3 tables. $8.00.

Aportacion de la Escuela Espanola a la Tecnica Endobronquial. Analisis Cronologica y Doctrinal. Conferencia pronunciada en la Real Academia Nacional de Medicina. *Dr. S. Garcia-Vicente.* Madrid, 1953. 43 pages, 10 figures, 1 table.

Die Peripheren Durchblutungsstörungen, 5., Umgearbeitete und Ergänzte Auflage. *Dr. Max Ratschow.* Dresden and Leipzig, Theodor Steinkopff, 1953. 408 pages, 119 figures.

Traité des Cardiopathies Congénitales. *E. Donzelot, F. D'Allaines, R. Heim de Balzac, C. Metianu, M. Durand, Ch. Dubost, M. Allary, N. Du Bouchet, A.-M. Emam-Zadé, J.-E. Escalle, B. Latscha, J. Le Brigand, and N. Oeconomos.* Paris, Masson et Cie, 1954. 1118 pages, 1155 figures. 14,650 fr.

Electrocardiographie Clinique. *J. Lenegre, G. Carouso, and H. Chevalier.* Paris, Masson et Cie, 1954. 810 pages, 341 figures. 7,600 fr.

L'Hypertension Artérielle Neuro-Hormonale. Rapports Presentes au XXIXe Congres Français de Medecine, Paris 1953. *President du Congres: Pr. M. Loeper.* Paris, Masson et Cie, 1953. 311 pages, 14 figures, 14 tables. 1,850 fr.

Thoracic Surgery, ed. 2. *Richard H. Sweet, M.D. Illustrations by Jorge Rodriguez Arroyo, M.D.* Philadelphia, Saunders, 1954. 381 pages, 159 figures.

Penicilinoterapia de la Sifilis Cardiovascular. Observaciones Clinicas Inmediatas Y a Largo Plazo Resultados Que se Basan en Estudios Histopatologicos. *Peralta V. Aurelio.* Tesis de Doctorado. Lima, Peru, 1953. 85 pages, 18 figures, 27 tables.

Die Objektive Stereoskopie an Röntgenbildern. Eine Diagnostische Methode. *Prof. Dr. A. Hasselwander.* Stuttgart, Georg Thieme, 1954. 187 pages, 125 tables. DM 27 ($6.40).

A Primer of Congestive Heart Failure. American Lectures in Internal Medicine #190. *George E. Burch, M.D.* Springfield, Ill., Charles C Thomas, 1954. 126 pages, 15 figures, 1 table. $4.00.

The Hepatic Circulation and Portal Hypertension. *Charles G. Child, III, M.D. In collaboration with Ward D. O'Sullivan, M.D., Mary Ann Payne, M.D., George R. Holswade, M.D., Roger Milnes, M.D., Arthur L. Gore, M.D., Daniel M. Hays, M.D., Roy D. McClure, Jr., M.D., Helena Gilder, M.D., Charles S. Harrison, M.D., David Barr, M.D., and Earl A. O'Neill, M.D.* Philadelphia, Saunders, 1954. 444 pages, 132 figures, 19 tables. $12.00.

Proceedings of the Annual Meeting, Council for High Blood Pressure Research, American Heart Association. May 15–16, 1953, Cleveland, Ohio. Volume II. *R. W. Sevy, Ph.D., Georges M. C. Masson, Ph.D., Simon Rodbard, M.D., D. M. Green, M.D., and George A. Perera, M.D.* New York, American Heart Association, 1954. 94 pages, 33 figures, 15 tables. $2.00.

1954 Medical Progress. A Review of Medical Advances During 1953. *Morris Fishbein, M.D., Editor.* New York, Blakiston, 1954. 345 pages. $5.00.

Psychosomatic Case Book. *Roy R. Grinker, M.D., and Fred P. Robbins, M.D.* New York, Blakiston, 1954. 346 pages. $6.50.

A Manual on Cardiac Resuscitation. *Robert M. Hosler, M.D., F.A.C.S.* Springfield, Ill. Charles C Thomas, 1954. 183 pages, 14 figures. $4.00.

The Uncommon Heart Diseases. *Nathaniel E.*

Reich, M.D. Springfield, Ill., Charles C Thomas, 1954. 516 pages, 110 figures, 35 tables. $10.50.

Cardiovascular Surgery. *Gerald H. Pratt, M.D.* Philadelphia, Lea and Febiger, 1954. 843 pages, 358 illustrations on 261 figures, 4 color plates, 52 tables. $15.00.

Eat, Think and Be Slender. *Leonid Kotkin, M.D., with the assistance of Fred Kerner.* New York, Hawthorn Books, 1954. 224 pages. $2.95.

Mayo Clinic Diet Manual. ed. 2. *The Committee on Dietetics of the Mayo Clinic.* Philadelphia, Saunders, 1954. 247 pages. $5.50.

Current Therapy 1954. Latest Approved Methods of Treatment for the Practicing Physician. *Howard F. Conn. M.D., Editor; Consulting Editors: M. Edward Davis, Vincent J. Derbes, Garfield G. Duncan, Hugh J. Jewett, William J. Kerr, Perrin H. Long, H. Houston Merritt, Paul A. O'Leary, Walter L. Palmer, Hobart A. Reimann, Cyrus C. Sturgis, and Robert H. Williams.* Philadelphia, Saunders, 1954. 898 pages. $11.00.

La Persistance du Canal Artériel et Son Traitement. *Michel Montouchet.* Annecy, France, Imprimerie Gardet, 1954. 199 pages. 1500 fr.

Diseases of the Liver. *Mitchell A. Spellberg, M.D., F.A.C.P.* New York, Grune & Stratton, 1954. 646 pages, 93 figures, 77 tables. $16.50.

Physiology in Diseases of the Heart and Lungs. Revised Edition. *Mark D. Altschule, M.D.* Cambridge, Mass., Harvard University Press, 1954. 554 pages. $7.50.

Digital Plethysmography. Introducing a Method for Recording Simultaneously the Time Course of the Rate of Blood Flow Into and Out of the Fingertips. *George E. Burch, M.D., F.A.C.P.* New York, Grune & Stratton, 1954. 134 pages, 83 figures. $5.00.

An Atlas of Congenital Anomalies of the Heart and Great Vessels. *Jesse E. Edwards, Thomas J. Dry, Robert L. Parker, Howard B. Burchell, Earl H. Wood, and Arthur H. Bulbulian.* Springfield, Ill., Charles C Thomas, 1954. 202 pages, 256 figures. $13.50.

Wine as Food and Medicine. *Salvatore P. Lucia, A. B., M.D., Sc.D., F.A.C.P.* New York, Blakiston, 1954. 149 pages, 4 tables. $3.00.

Electrocardiography. *E. Grey Dimond, M.D.* St. Louis, Mosby, 1954. 261 pages, 272 figures. $14.00.

Handbook of Cardiology for Nurses, ed. 2. *Walter Modell, M.D., F.A.C.P., and Doris R. Schwartz, B.S., R.N.* New York, Springer, 1954. 320 pages, 5 figures. $4.25.

BOOK REVIEWS

The Motion of the Heart. The Story of Cardiovascular Research. *Blake Cabot.* New York, Harper, 1954. 173 pages. $2.00.

The primary purpose of this book is to present to the public a comprehensible picture of the scope of present-day research in diseases of the heart and circulation, with examples of the manner in which important discoveries have been made in the past and a summary of the major problems waiting solution. Blake Cabot has done an excellent job, and the American Heart Association is to be commended for having underwritten the project. The lay reader will find the volume packed with fascinating facts, and there are few physicians to whom it will not be both interesting and instructive. For medical people who are requested to speak on cardiovascular subjects before nonmedical audiences, its pages are rich with suggestions as to source material and models of effective presentation.

A brief introductory chapter presents a panoramic picture of cardiovascular research across the nation today. This is followed by a discussion of the evolution of our knowledge of the circulation, the mechanism of the heart beat and cardiac arrhythmias, and the functions of capillaries. In each instance, the story is brought down to the latest technics and discoveries. Next is a chapter which deals expertly with the coronary circulation, recent studies on the etiology of coronary atherosclerosis, and the importance of anticoagulant drugs.

A review of hypertension extends from the observations of Stephen Hales to the introduction of *Rauwolfia serpentina*. The pathogenesis and prophylaxis of rheumatic fever is presented in an illuminating manner, and there is a brief account of mitral valve surgery. Congestive heart failure is summarized in terms readily understandable to the nonprofessional reader. The discussion of the metabolism of the myocardium cannot fail to convince the layman and the skeptical physician of the fascination and importance of basic research. The surgical treatment of congenital cardiovascular anomalies is considered in a restrained manner, laudably free from melodrama.

In conclusion, one must agree with Dr. H. M. Marvin, who states in the preface, "For all who wish to extend the boundaries of their knowledge, the reading of this book will be a richly rewarding experience."

A. Carlton Ernstene

Heart and Circulation, Diagnosis and Treatment. *Meyer Sclar, M.D., F.A.C.C.* New York, Fraben Press, 1953. 357 pages, 52 figures. $7.50.

Caveat emptor, because there is no thief like a bad book. This one contains less cardiovascular information than a standard textbook of medicine and on some subjects less than a medical dictionary. The information is superficial, distorted and not infrequently erroneous. The following samples characterize its scholarship and style: the apex impulse may be displaced in tumor of the aorta; the transverse diameter of the heart is of great importance; the chief use of the electrocardiogram is recognition of coronary disease; the electrocardiogram measures the electrical potential which occurs as a result of muscular contraction; precordial leads detect coronary pathology; S.O.S. signal is dyspnea after exertion; premature beats after middle age denote serious heart disease; rheumatic fever is caused by the beta hemolytic streptococcus; cortisone is used for subacute bacterial endocarditis; the signs of mitral stenosis are rapid respirations; if one ventricle shows considerable hypertrophy, the electrocardiogram is suggestive.

The reproductions of the few roentgenograms are primitive and covered with ink marks representing the author's concept of cardiac silhouettes. Several of the few electrocardiographic reproductions are either mislabeled (e.g., Wenckebach) or a lead is mounted upside down. Left bundle branch is defined loosely and by limb leads alone. Differential diagnosis consists of naming several diseases. The discussion of treatment, for the most part, consists of vague generalities.

LOUIS A. SOLOFF

Cardiovascular Surgery. *Gerald H. Pratt. M.D., F.A.C.S.* Philadelphia, Lea & Febiger, 1954. 843 pages, 358 illustrations on 261 figures, 4 color plates, 52 tables. $15.00.

In a recent editorial, Norman Cousins made the point that at least two experiences are shared by every serious writer. The first is the yearning or determination to write his heart out in one Big Book. The second is the dread of finality, not knowing when the book is finished and being reluctant to part with it even after he managed to end it. The monograph of Dr. Gerald H. Pratt is truly a Big Book. It is broad in scope in that it includes both cardiac and peripheral vascular surgery together with the pathology and medical treatment of cardiovascular disease. It is voluminous, containing 843 pages, with 358 illustrations on 261 figures, and four color plates. Some of its sections, notably the one on hypertension and on the lymphatic circulatory system, are brief, concise and to the point. Others, unfortunately, are verbose, redundant, with disturbing errors in spelling too numerous to mention. The frequent use of expressions like, "surgeon responsibility," "anesthesia selection" or "brain circulation cessation" are disturbing but of course could be readily corrected.

The author likes to coin expressions which may seem unfamiliar to the readers. He uses "antithrombotic" instead of anticoagulant therapy and uses, "analogous" instead of autogenous vein grafts. He calls the humoral vasoconstrictor, "spastin."

One may question the value of creating arteriovenous fistulas to increase circulation to the brain or to decompress an aneurysm. The simultaneous use of anticoagulants and sympathetic blocks is advised on the basis of 2152 paravertebral injections without hemorrhage; truly an impressive record but hardly to be advised to surgeons or anesthesiologists.

There is little emphasis on the myogenic contracture of arteries around a thrombus or embolus, and there is no mention of prophylactic femoral vein ligation prior to major amputation. Nevertheless most of his statements are based on extensive clinical experience and represent the practice of his vascular clinic.

The purpose of this contribution, as stated in the preface, is to bring to surgeons, internists and students a summary of accepted or acceptable treatment for cardiovascular lesions. Generally speaking, the author has succeeded in this heroic task. The road from aortic regurgitation through portal hypertension to arterial varices (a syndrome not too well established) is truly arduous, and he has covered an immense field with excellent illustrations and a profuse bibliography. With more careful editing and a tighter organization of much overlapping material this volume could be shortened and made more useful in future editions.

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SECOND WORLD CONGRESS OF CARDIOLOGY

A total of over 3,100 registrants from 50 nations attended the Second World Congress of Cardiology which was combined with the Twenty-Seventh Scientific Sessions of the American Heart Association at the National Guard Armory in Washington, D. C., September 12–17. About one-third were physicians from abroad.

Dr. Paul D. White, Boston, who served as President of the Congress, was elected President of the International Society of Cardiology which sponsors these Congresses. He succeeded Dr. Charles Laubry of Paris, who has held the post for the past four years, and who presided over the first international cardiology congress in Paris in 1950. Other officers named at a meeting of the Society's Council include: First Vice President, Prof. Ignacio Chavez, Mexico City; Second Vice President, Prof. D. E. Bedford, London; Secretary-General, Prof. Pierre Duchosal, Geneva; Treasurer, Dr. Louis N. Katz, Chicago; Assistant Secretary, Dr. John Palmer, Montreal.

Brussels, Belgium, was chosen as the scene for the Third World Congress of Cardiology to be held in 1958. The Inter-European Congress of Cardiology will be held in Stockholm in 1956, and the Inter-American Congress of Cardiology will convene in Havana in the same year.

The next regular Scientific Sessions of the American Heart Association will be held in conjunction with the Association's Annual Meeting, October 22–27, 1955, at the Jung Hotel in New Orleans.

Copies of the printed program for the Second World Congress of Cardiology are still available at $3.00 a copy from the American Heart Association, 44 East 23rd Street, New York 10, N. Y. The 559-page volume contains abstracts of papers presented at the formal scientific sessions. The abstracts are printed in English, with translations in Interlingua, a new international language, and in some cases in their original language.

NEW OFFICERS OF SCIENTIFIC COUNCIL

The following officers of the Scientific Council of the American Heart Association were named at a meeting held during the Second World Congress of Cardiology in Washington. Robert L. King, M.D., Seattle, has automatically assumed the Chairmanship of the Council as the immediate Past President of the Association. Dr. King is Chief of Medical Service of the Virginia Mason Hospital in Seattle, Clinical Associate Professor of Medicine at the University of Washington School of Medicine and Consultant in Cardiology to the Department of Health, Territory of Alaska.

Eugene Stead, M.D., Professor of Medicine at Duke University School of Medicine, Durham, N. C., was named Vice Chairman, and A. Carlton Ernstene, M.D., Chief of Medicine at the Cleveland Clinic, Cleveland, was named Secretary. Robert Wilkins, M.D., Associate Professor of Medicine at Boston University, and Hans Hecht, M.D., Associate Professor of Medicine, University of Utah College of Medicine, Salt Lake City, were elected to the Executive Committee of the Council.

"ATLAS OF CONGENITAL CARDIAC DISEASE," REPRINTED

In response to numerous requests from physicians, students, scientific workers and libraries throughout the world, the American Heart Association has reprinted the "Atlas of Congenital Cardiac Disease," by Dr. Maude F. Abbott. This classic monograph, a critical analysis of 1000 cases of congenital cardiac anomalies, was first published by the Associa-

tion in 1936. Long since out of print, it has now been reprinted in a limited edition of 1500 numbered copies exactly as it appeared originally.

The work of Dr. Maude Abbott, who died in 1940, served to bridge the gap between the previous unsystematic and largely descriptive knowledge of congenital cardiac defects and the present era of precise diagnosis and dramatic surgery.

The monograph was published largely at the suggestion of and with the encouragement of Dr. William W. Francis of the Osler Library, McGill University, Montreal, and with the permission of the executors of Dr. Abbott's estate.

The volume, which was printed by Peter F. Mallon, Inc., Long Island City, is available at a cost of $5.00. Copies may be obtained from the National Office of the American Heart Association or through affiliated Heart Associations and medical booksellers.

INTERPRETATION OF ARRHYTHMIAS

A course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital, December 13–16, by Louis N. Katz, M.D., Richard Langendorf, M.D. and Alfred Pick, M.D. This is an advanced course intended only for experienced electrocardiographers. The class will meet daily from 9:00 a.m. to 5:00 p.m.

Further information and a copy of the lecture schedule may be obtained from Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

MEETINGS CALENDAR

Nov. 10–12: Seventh Annual Conference on Electrical Techniques in Medicine and Biology, featuring two sessions devoted to circulation and cardiology and on electrical properties of biological materials; Morrison Hotel, Chicago; Herman P. Schwan, Hospital of the University of Pennsylvania, Phila. 4.

Nov. 12–13: American Geriatrics Society, Graduate Symposium on Geriatric Medicine, Roosevelt Hotel, New York City.

Nov. 29–Dec. 2: American Medical Association, Clinical Meeting, Miami; George F. Lull, M.D., Secretary, 535 North Dearborn St., Chicago 10, Ill.

The New England Cardiovascular Society

Scientific Program for 1954–1955

(All meetings will be held in the Morse Auditorium, Museum of Science, Science Park, Boston, at 8:00 p.m.)

Nov. 15, 1954: Boston City Hospital, Laurence B. Ellis, M.D.; Massachusetts General Hospital, Edward F. Bland, M.D.

Jan. 3, 1955: Peter Bent Brigham Hospital, Samuel A. Levine, M.D.; Invited Papers from New England, Dr Bland

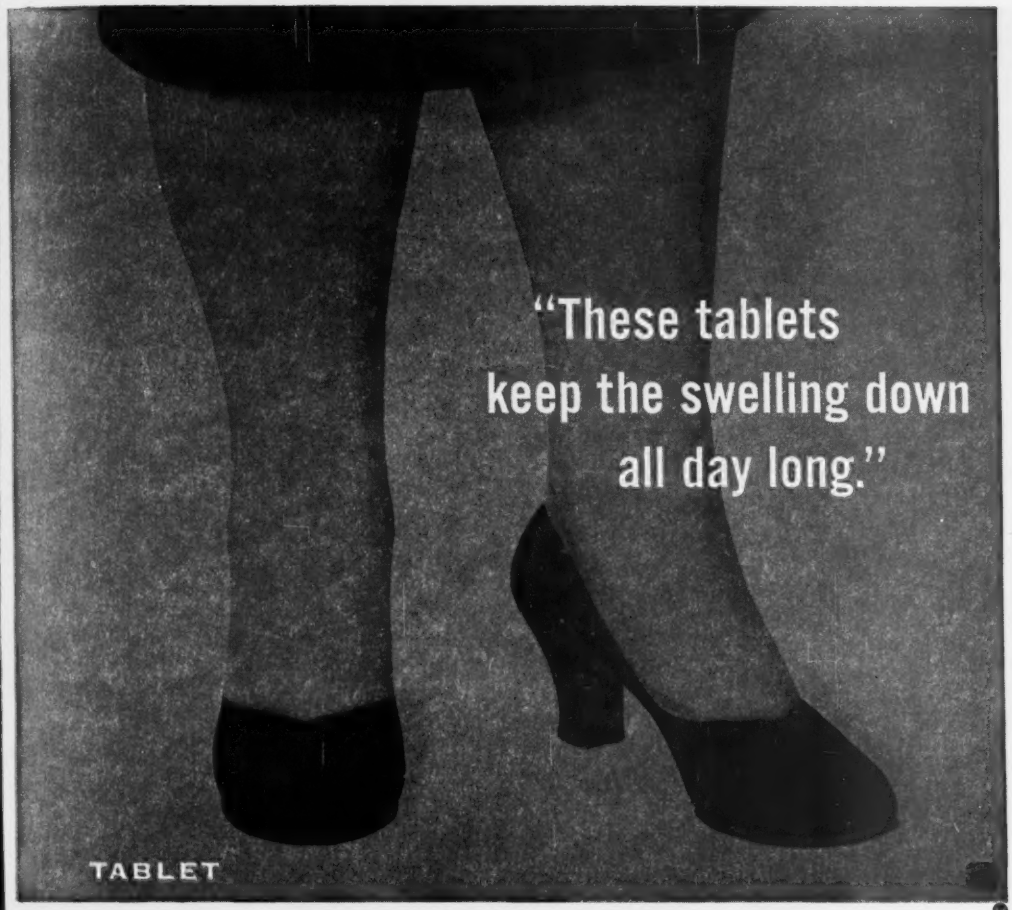
Feb. 7, 1955: Beth Israel Hospital, Herrman L. Blumgart, M.D.; Massachusetts Memorial Hospitals, Robert W. Wilkins, M.D.

Mar. 7, 1955: New England Center Hospital, Samuel Proger, M.D.; Children's Medical Center, Benedict F. Massell, M.D.

May 9, 1955: The Henry Jackson Lecture

ASSOCIATION GRANTS-IN-AID

Applications for Research Grants-in-Aid for the 1955–56 fiscal year must be received on or before Dec. 1, 1954. Grants are made to nonprofit institutions in direct support of a particular investigator, for a specific program of research under his direction. Grants are awarded in support of research in the cardiovascular field or basic sciences related to it in amounts up to $10,000 per annum for periods of one or more years. Information and application forms may be obtained from the Association's Medical Director.



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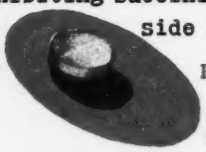

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